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THE PARATHYROID GLANDS

II. A HISTOLOGIC STUDY OF PARATHYROID ADENOMA

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For the past few years the various phases of the abnormal body states arising as a result of a paucity or an excess of the secretion of the parathyroid glands have intrigued investigators in all divisions of medical science. Many aspects of the problem have been studied and solved by the cooperation of physiologists, biochemists, endocrinologists, roentgenologists and surgeons. There remain, however, the pathologic study and classification of the parathyroid glands from patients who have suffered from an excess or abnormal secretion of these glands. At the time this study was undertaken, no acceptable classification of parathyroid tumors was available, but during the course of our investigations Castleman and Mallory [1] presented their work on this phase of the problem. In this report the workers collected from the literature and summarized 160 cases of disorders that were proved to be or that were probably hyperparathyroidism. Since this summary contains all the important data and is readily available, our work covering these cases has been deleted. To these cases Castleman and Mallory added 25 of their own, making a total of 185. The greatest numbers of cases previously reported were 5 by Hunter and Turnbull [2] and 6 by Bergstrand.[3]

HISTORY

The principal points of historical interest concerning the discovery and development of knowledge of the normal gland have been reviewed in another publication.[4] A large number of papers have been written

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1. Castleman, B., and Mallory, T. B.: Am. J. Path. **11**:1, 1935.
2. Hunter, D., and Turnbull, H. M.: Brit. J. Surg. **19**:203, 1931.
3. Bergstrand, H.: Acta med. Scandinav. **54**:539, 1921; Endocrinology **6**:477, 1922; Acta path. et microbiol. Scandinav. **5**:52, 1928; Acta med. Scandinav. **76**:128, 1931; Am. J. Cancer **21**:581, 1934.
4. Morgan, J. R. E.: Arch. Path., to be published.

on the various aspects of parathyroid disease, and since many excellent historical reviews of the subject are readily available further repetition is unnecessary. It is of interest, however, to note that the first parathyroid tumor was not described until 1900 (de Santi [5]), and it was not until 1925 that Mandl [6] definitely related hyperparathyroidism to generalized osteitis fibrosa cystica. Among the more comprehensive writings are those of Albright and his co-workers,[7] Collip,[8] Hunter and Turnbull,[2] Bergstrand,[3] Welti,[9] Jung,[10] Churchill and Cope,[11] Compere [12] and Castleman and Mallory.[1] The recent publication by the latter two investigators contains an excellent review of the literature to date.

REPORT OF CASES

This report presents 6 cases of parathyroid tumor with associated hyperparathyroidism. Five of the cases were in patients of the Lahey Clinic, and in each one Dr. Frank H. Lahey found and removed a parathyroid tumor. The sixth case was discovered only at autopsy, the roentgenologic observations having been misinterpreted owing to an associated carcinoma of the breast.

CASE 1.—A white woman, aged 62, entered the New England Deaconess Hospital for treatment of vulvovaginitis. Routine examination revealed marked kyphosis, loss of stature and rarefaction of all bones except those of the skull and feet. The serum calcium was 14 mg. per hundred cubic centimeters; the phosphorus, 2 mg., and the phosphatase elevated. The calcium balance was negative. Hyperparathyroidism was diagnosed.

There was no palpable tumor, but an exploratory operation revealed below the lower left lobe of the thyroid a mass which extended down into the anterior part of the mediastinum and was distinctly separated from the thyroid except for blood vessels and areolar tissue. On the third day after operation the serum calcium was 9.8 mg., and mild tetany was present. Later the serum calcium fell to 7.1 mg., and the phosphorus rose to 2.4 mg. With adequate treatment the patient made a good recovery and was discharged four weeks after operation.

5. de Santi: Internat. Centralbl. f. Laryng. u. Rhin. **16**:546, 1900.

6. Mandl, F.: Wien. klin. Wchnschr. **38**:1434, 1925; Zentralbl. f. Chir. **53**:260, 1926.

7. Albright, F.; Bloomberg, E.; Castleman, B., and Churchill, E. D.: Arch. Int. Med. **54**:315, 1934. Albright, F.; Baird, P. C.; Cope, O., and Bloomberg, E.: Am. J. M. Sc. **187**:49, 1934. Albright, F.; Aub, J. C., and Bauer, W.: J. A. M. A. **102**:1276, 1934. Albright, F.: New England J. Med. **209**:476, 1933. Bauer, W.; Albright, F., and Aub, J. C.: J. Clin. Investigation **8**:229, 1930.

8. Collip, J. B.: J. Biol. Chem. **63**:395, 1925; Medicine **5**:1, 1926; Canad. M. A. J. **24**:646, 1931.

9. Welti, H.: Chirurgie des parathyroïdes, in Rapport, Association française de Chirurgie, XLII. Congrès français de Chirurgie, Paris, Brodard & Taupin, 1933.

10. Jung, A.: Chirurgie des parathyroïdes, in Rapport, Association française de Chirurgie, XLII. Congrès français de Chirurgie, Paris, Brodard & Taupin, 1933.

11. Churchill, E. D., and Cope, O.: Surg., Gynec. & Obst. **58**:255, 1934.

12. Compere, E. L.: Surg., Gynec. & Obst. **50**:783, 1930.

Gross Description.—The tumor mass measured 3 by 2 by 1.5 cm., was well encapsulated and of a yellowish-pink mottled color. The tissue was soft and on section bulged slightly above the cut surface. Sections for microscopic study were taken from each end of the tumor, one of which was a deeper yellow than the other.

Microscopic Description of Section A.—Section A (fig. 1 *A*) consisted almost entirely of transitional oxyphil cells which were slightly larger than normal,

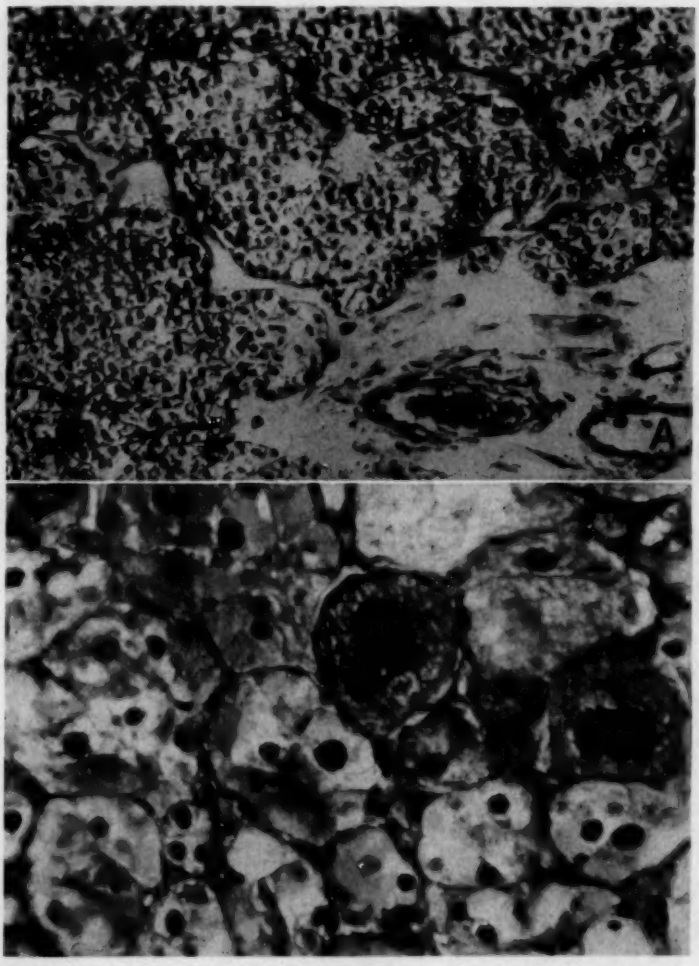

Fig. 1 (case 1).—*A*, parathyroid adenoma; × 275. Note the uniformity of the cells and the irregularity of the fibrous tissue. This is a hematoxylin eosin preparation. The granules are unstained. *B*, marked cellular variability; × 825. Note the nuclear gigantism and multiplicity.

varying from 9 to 16 microns in diameter, with the average cell measuring about 12 microns. The cells varied in shape from round to polygonal, with the cell membrane usually distinct. With the modified Mallory stain the cytoplasm

contained a variable amount of reddish granular material. The nuclei were slightly larger than normal and, though chiefly of the dark type, other transitional forms were also present. Scattered throughout the section were a few principal and oxyphil cell forms. The latter cells had an average diameter of about 18 microns and except for a slight increase in size and diminution in intensity of granular staining were similar to the normal oxyphil cell.

The stroma was irregular in amount and distribution, being thick and collagenous in some areas and thin and stringy in others. This fibrous tissue divided the cells into irregular cords and clumps, with a few alveolar structures also present. The acinar walls were composed of transitional oxyphils with an occasional mature oxyphil form and, though many acini were empty, some contained a clear colloid substance. The vascular network showed a moderate increase in amount and an irregularity of vessel caliber and distribution. A few fat cells, singly and in small groups, were also scattered throughout the tissue.

Summary: This section of the tumor was composed chiefly of transitional oxyphil forms with a few normal principal and oxyphil cells also present. There was moderate and irregular increase in the vascular supply and fibrous tissue stroma. The cells contained no mitotic figures nor did they present evidence of active proliferation.

Diagnosis: Transitional oxyphil cell adenoma.

Microscopic Description of Section B.—The cells of this section (fig. 1*B*) were so heterogeneous and variable that their description is difficult. The most striking feature was the magnitude of the cells, many of which measured up to 50 microns in diameter, with the average cell diameter being about 25 microns. The amount of cytoplasmic granularity was extremely variable, ranging from a closely packed mass of acidophilic granules to a perfectly clear ballooned cell. The nuclei presented the most distinctive features, being chiefly large, round or oval and taking a pale stain. Most of the nuclear chromatin consisted of finely divided sandlike particles, but a few pyknotic nuclei were also present. The nuclei measured from 6 to 20 microns in diameter with an average of about 12 microns, and each contained from 1 to 4 bright red irregular nuclei which were slightly larger than normal. Many of the cells had multiple nuclei, the number ranging from 2 to 6.

The fibrous tissue stroma presented a slight increase in amount and was irregularly distributed. The cells presented a protean arrangement with no alveolar formation. As in the other section, the vascular supply was increased in amount and irregular in distribution.

Summary: The majority of cells most closely resembled the transitional oxyphil type but showed giant forms with nuclear gigantism and multiplicity. There were no mitotic figures, but the multinucleated cells were indicative of amitotic division. There was a slight irregular increase in fibrous tissue and vascular supply.

Though the two sections were taken from the same tumor and classified as being of the same type (transitional oxyphil), there was a marked variation in cell forms. Section B showed a much greater variation in cell types from one area to another and often within the confines of a single low power field.

Diagnosis: Transitional oxyphil cell adenoma.

Case 2.—A white woman, aged 52, entered the New England Baptist Hospital with the complaint of pain in the knees and neck and partial loss of function of various joints. Examination revealed marked arthritic changes of the cervical vertebrae, decalcification of the femurs and crepitation and thickening of the synovial membrane of the knee joints. The serum calcium was 12.5 mg., and

the phosphorus and phosphatase were within normal limits. The calcium balance was negative. The diagnosis was atrophic arthritis and hyperparathyroidism.

There was no palpable mass, but at operation the right inferior parathyroid was found to be greatly enlarged. On the second day following operation the serum calcium was 10.9 mg. and the phosphorus 2.8 mg. The patient did not have tetany and on discharge, ten days after operation, had normal amounts of serum calcium and phosphorus.

Gross Description.—The tumor consisted of a rounded, fully encapsulated mass of tissue measuring 1 cm. in diameter. It was moderately firm in consistency and of a reddish-brown mottled color. Section revealed a reddish-brown mottled moist surface which bulged slightly.

Microscopic Description.—All cells of this tumor corresponded to the types seen in the normal gland. There was, however, a great preponderance of oxyphilic forms, both transitional and mature, with comparatively few principal cells. Except for an occasional *wasserhelle* form, all cells contained red granules which stained slightly lighter than normal. Virtually every cell was larger than its normal prototype, with many of the oxyphil forms measuring up to 30 microns in diameter. The nuclei were for the most part large, round and swollen, with a light staining reaction, and from 1 to 3 prominent, deeply acidophilic nucleoli. An occasional oxyphil form was present which contained 2 or 3 large pale nuclei, but no mitotic figures were seen.

The fibrous tissue stroma was in some areas irregularly thickened and in others stringy and less abundant. This tissue divided the cells into irregular clumps and masses with no definite arrangement or alveolar structures present. The sinusoidal capillaries showed a marked variation in caliber and regularity of distribution.

Summary: Most cells were of the transitional oxyphil type with a slight but definite increase in size. Cellular gigantism and nuclear multiplicity were present but not frequent. There was an irregular increase in fibrous tissue and vascular supply. No mitotic division was demonstrable.

Diagnosis: Transitional oxyphil cell adenoma.

Case 3.—A white woman, aged 48, entered the New England Baptist Hospital with a palpable adenomatous goiter and a complaint of nervousness, pain in the legs and a loss of 40 pounds (18.1 Kg.) in weight over a period of ten years. During the six years previous to admission she had suffered from three spontaneous fractures. Physical examination revealed kyphosis, lordosis and scoliosis, shortening and inversion of the right leg, compression of vertebrae, typical roentgenologic evidence of generalized osteitis fibrosa cystica, adenomatous goiter, generalized arteriosclerosis, hypertension, etc. The serum calcium was 11.3 mg. and the phosphorus 3 mg.

At operation two adenomatous nodules were removed but were proved by frozen section to be thyroid tissue. Further search revealed a firm hard nodule in the substance of the right upper pole of the thyroid, which on section proved to be parathyroid tissue. Following parathyroidectomy the serum calcium fell to 10 mg. and the phosphorus to 1.9 mg. The patient had a normal convalescence and was discharged sixteen days after operation.

Gross Description.—The specimen consisted of a small rounded piece of firm reddish-brown mottled tissue which measured 0.7 cm. in diameter. Section revealed a homogeneous tissue with a moist, smooth, reddish-brown mottled surface.

Microscopic Description.—The tissue consisted chiefly of dark principal and transitional oxyphil cell forms with but few light principal and mature oxyphil

cells present. The cells showed a slight but definite increase in size, and scattered throughout the tissue were small irregular clumps of giant transitional oxyphil forms which measured up to 30 microns in diameter. These cells contained from 1 to 4 nuclei with prominent nucleoli and measured from 6 to 20 microns in diameter. The intercellular fibrous connective tissue stroma was markedly variable in amount and distribution, being in broad collagenous sheets in some areas and thin stringy wisps in others. The cells were divided into irregular clumps and groups with no appreciable attempt at follicle formation. The vascular supply through the dilated sinusoidal capillaries was irregularly distributed.

Summary: Though the majority of the cells were of the transitional oxyphil type, the presence of large numbers of dark principal cells, which were also transitional forms, indicated that this tumor more closely approached the normal gland cell type. Cell hypertrophy with nuclear gigantism and multiplicity was a prominent feature. The fibrous tissue stroma and vascular supply were both increased and irregularly distributed throughout. There was no mitotic activity, but amitotic division was present.

Diagnosis: Transitional oxyphil cell adenoma.

CASE 4.—A white woman, aged 52, was admitted to the New England Deaconess Hospital with a history of intermittent pain in the left epigastric region for sixteen years. Examination revealed an irritable colon and stricture of the anal sphincter. Routine investigation showed an anterolateral bowing of the left tibia, narrowing and rarefaction of the vertebrae, shortening of the right leg and mottling of the bones of the vault of the skull, ilium and sacrum. The serum calcium was 14.1 mg. and the phosphorus 2.1 mg.

An exploratory operation was performed, and a tumor the size of a lima bean was found in the position of the right inferior parathyroid. During convalescence the serum calcium fell to as low as 7.8 mg., and a slight degree of tetany was elicited. Recovery was uneventful, and the patient was discharged with normal amounts of serum calcium and phosphorus.

Gross Description.—The specimen consisted of an encapsulated bean-shaped piece of soft, yellowish amber-colored tissue which measured 1.5 cm. in its greatest diameter. On section the tumor presented a moist homogeneous yellow surface.

Microscopic Description.—The majority of the cells in this tumor most closely resembled the pale principal type. Though a few dark principal cells were present, there were no mature oxyphils and only a few transitional oxyphil forms. Many of the cells were of normal size, but the majority had a slightly larger diameter. The cytoplasmic detail was poor, and the cell outline was often indistinct. The cell diameter measured up to 14 microns, and the prominent nuclei measured up to 9 microns. Most of the nuclei were larger than normal, pale staining and finely granular. Only occasionally did a cell contain more than a single nucleus.

There was a slight, irregularly distributed increase in fibrous connective tissue stroma, and though most of the cells presented a protean arrangement, many large alveoli were present. The vascular supply consisted of large sinusoidal capillaries with a marked variability in caliber and distribution. These thin-walled structures were very fragile, and in many areas they had been ruptured by the operative manipulations, producing small areas of fresh hemorrhage throughout the tissue.

Summary: The tumor consisted almost entirely of large pale principal cell forms among which no true giant cells were present, and only an occasional example of nuclear multiplicity was noted. There was, however, a fairly well marked

variation in cell and nuclear size. There was a slight irregular increase in fibrous tissue as well as a marked increase in vascularity. No mitotic figures were present, and only an occasional evidence of amitotic division was noted.

Diagnosis: Principal cell adenoma.

CASE 5.—A white woman, aged 45, entered the New England Deaconess Hospital with the complaint of progressive loss of stature and pain in the back and knees increasing in severity for two years. Multiple pains and aches had also been present for six months. Examination revealed marked kyphosis at the level of the eighth dorsal vertebra, knee joints not remarkable and general physical condition good. Roentgenologic evidence of generalized osteitis fibrosa cystica was demonstrated. The serum calcium was 14.4 mg. and the phosphorus 2.4 mg.

No tumor was palpable, but when an exploratory operation was performed a large tumor occupying the site of the right lower parathyroid was removed. Convalescence was uneventful with no severe symptoms of hypoparathyroidism. The serum calcium fell to 7.5 mg. and the phosphorus to 1 mg. six days after operation. When the patient was discharged on the twelfth day the serum calcium had risen to 8.9 mg. and the phosphorus to 1.5 mg.

Gross Description.—The specimen consisted of an encapsulated tumor mass measuring 3.5 by 2.4 by 1 cm. It was soft and yellowish brown, and showed a small subcapsular hemorrhage. The cut surface was light brown and moist.

Microscopic Description.—The tissue was almost entirely composed of transitional oxyphil forms which showed a slight variability in size, with a few large and irregular cells present. The average diameter was about 12 microns with the nuclei averaging about 7.5 microns. The cytoplasm contained a variable amount of granular material ranging from an occasional red granule to a solidly packed granular mass. Nuclear gigantism and multiplicity were present but rare.

There was only a slight irregular increase in the fibrous tissue stroma which divided the cells into irregular groups. A few alveolar structures lined by tall columnar transitional oxyphil forms were noted. These acini contained no secretory product, but some were filled by recent hemorrhage, probably of traumatic origin. The sinusoidal capillaries showed a marked variability of caliber, engorgement and distribution.

Summary: The tumor consisted chiefly of transitional oxyphil cells which showed a considerable variability in size. There was a generalized increase in diameter of virtually all cells and nuclei. Nuclear gigantism and multiplicity were present rarely. There was no mitotic activity, but amitotic division was demonstrable.

Diagnosis: Transitional oxyphil cell adenoma.

CASE 6.—A white woman, aged 55, first noted a small symptomless lump in the right breast about one year before death. When first seen at the Huntington Memorial Hospital she had an extensive carcinoma of the breast with metastases to the axillary lymph nodes, the bones of the skull, spine and pelvis and both lungs. She was given a course of roentgen treatments with some relief from pain. Her admission to the Pondville State Hospital was essentially for terminal care. At this institution she was given further radiation treatment but her course was progressively downhill. Roentgen films showed a widespread irregular rarefaction of bone which in view of the primary tumor was interpreted as metastatic tumor lesions. No studies of the blood were done.

Autopsy, performed by Dr. Cecil Krakower, revealed the fact that, though several foci of bone metastases were present, most of the osseous lesions were tumor-free. They were diagnosed as generalized osteitis fibrosa cystica. A care-

ful search of the thyroid region revealed a tumor in the position of the right superior parathyroid. The other parathyroids were not noted.

Gross Description.—The tumor consisted of a mass of soft reddish-brown mottled tissue which measured 1.7 cm. in length and 0.9 cm. in its greatest diameter. At one end of the tissue was a small mass about 0.7 cm. in diameter

Fig. 2 (case 6).—Parathyroid adenoma; × 15. A photomicrograph of a section of the whole tumor showing two large portions and a rim of normal tissue at the top. Note the size, number and irregular distribution of the vessels.

which was of a more yellowish-brown color and resembled normal parathyroid tissue.

Microscopic Description.—The tumor could be conveniently divided into three portions (fig. 2). The largest part consisted almost entirely of mature oxyphil cells, the exception being an occasional transitional oxyphil in which there was a

small perinuclear clear space with a slight diminution in cytoplasmic granularity. The oxyphil cells were of a fairly uniform size throughout and measured from 12 to 16 microns in their greatest diameters. The cytoplasm was filled with strongly acidophilic granules which were more closely packed in some than in others. The nuclei varied from 4 to 8 microns in diameter, with the average being about 6 microns. No true giant nuclei were present, but several cells contained 2 or 3 nuclear structures.

There was a slight increase in fibrous tissue stroma, also a slight variation in capillary caliber and distribution. The cells were arranged in solid protean masses, cords and alveolar structures, with many of the latter being large, dilated and cystic in appearance.

The second portion consisted of a smaller mass of cells situated at one end of the section and separated from it by a small amount of fibrous tissue.

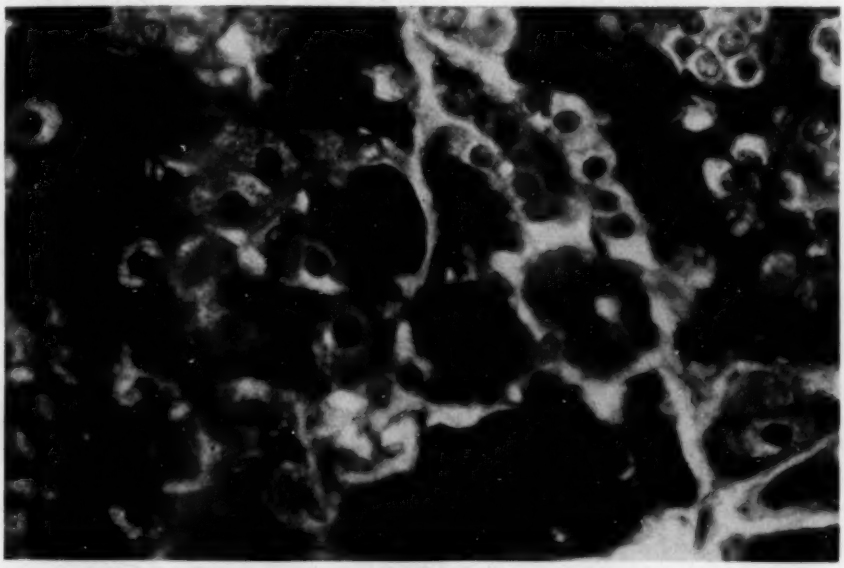

Fig. 3 (case 6).—Parathyroid adenoma; × 1,500. The smaller mass is shown. Note the mature and transitional oxyphil cells.

The cells of this area consisted of principal cell forms, throughout which were scattered large and small groups of oxyphils morphologically similar to those in the larger mass (fig. 3). The cellular arrangement, fibrous tissue and vascular supply were similar to those already described.

The third portion consisted of a narrow rim of tissue composed of principal cells and separated from the tumor by a small amount of fibrous tissue.

Summary: The main tumor mass consisted of cells which were definitely oxyphilic in type. There was a slight increase in fibrous tissue stroma and vascular supply with irregularity of distribution. Nuclear and cellular gigantism was not present, but multiple nucleated cells were noted. The smaller portion of tissue consisted chiefly of normal pale principal cells with many oxyphils and transitional forms scattered throughout. The outer rim of normal-appearing tissue suggested that this portion represented the original glandular tissue, with the other portions constituting an adenomatous neoplasia. The absence of cellular

compression was, however, not in favor of this assumption. The weight of evidence seemed to favor the diagnosis of adenoma.

Diagnosis: Oxyphil cell adenoma.

SUMMARY OF REPORT OF CASES

The more interesting features of the cases (table) are as follows:

All the patients were women from 45 to 62 years of age, the average being 52.3 years. Each one presented roentgenologic evidence of fibrocystic bone disease while none had nephrolithiasis. The preoperative serum calcium determinations ranged from 11.3 to 14.4 mg., and it was noted that in the cases with the higher preoperative values the serum calcium fell to lower levels after parathyroidectomy. Though probably of no significance, it is interesting to observe that 5 of the tumors occurred on the right side and 4 in the lower glands. Four of the tumors were classified as transitional oxyphil cell adenomas, 1 as a principal cell adenoma and 1 as a mature oxyphil adenoma.

Considering cases 1, 2, 3 and 5, in all of which the diagnosis was transitional oxyphil cell adenoma, there appears to be a direct relationship between the size of the tumor and the preoperative level of the serum calcium. There is, however, not sufficient evidence to merit the drawing of any conclusions from the observation.

COMMENT

Castleman and Mallory [1] divided benign parathyroid tumors into two groups: adenoma and hyperplasia. By the classification of these workers the cases reported in the foregoing section, with the possible exception of case 6, were all instances of adenoma.

The most prominent feature of all these tumors was the generalized cellular enlargement. Though cells of normal dimensions were seen, the size of the average tumor cell was many times that of the normal. Since the only true estimation of cell size is determined by computation of its volume, a considerable time was devoted to this study. The equation $V = 1/6\ \pi D^3$ was used, the value D being estimated as accurately as possible after the study of serial sections of the tumors. In case 1 many of the larger cells were found to be more than eighty times the volume of the normal cell. It was also found that if the tumor were due to a straight hypertrophy of preexisting cells its size could in many cases be accounted for by this hypertrophy.

Hypertrophy alone, however, is not sufficient to explain the many histopathologic aspects. Nuclear multiplicity and gigantism were noted in varying degrees in all the tumors, the number ranging from 2 to 6 and the size up to 20 microns. The nuclear abnormalities are interpreted as indicative of amitotic division, the etiologic factor of which is unknown. Many of the nuclei contained from 2 to 5 prominent large round nucleoli, irregularly distributed (fig. 1*B*).

Summary of Data on Six Cases of Parathyroid Adenoma

Case	Age, Yrs.	Sex	Duration of Symptoms, Yrs.	Roentgen Observations		Serum Calcium and Phosphorus				Tumor			Cells		Nuclei		Cell Volume (n = 267.99 Cu. Microns)
						Preoperative		Postoperative									
				Bone Changes	Renal Stone	Calcium, Mg.	Phosphorus, Mg.	Calcium, Mg.	Phosphorus, Mg.	Site	Size, Cm.	Cell Type	Variation, Microns	Mean, Microns	Variation, Microns	Mean, Microns	
1.....	62	♀	5	+	0	14.0	2.0	7.8	2.4	LL	3 by 2 by 1.5	A. Transitional oxyphil	9-16	13	7- 9	8	1,149.76
												B. Transitional oxyphil	10-50	24	6-20	11	7,232.89
2.....	52	♀	Several	+	0	12.5	2.5	10.9	2.8	RL	1.0 diameter	Transitional oxyphil	7-30	12	6-14	8.5	894.32
3.....	48	♀	10	+	0	11.3	3.0	10.0	1.9	RU	0.7 diameter	Transitional oxyphil	7-30	10	6-20	8	523.33
4.....	52	♀	4	+	0	14.1	2.1	7.8	3.7	RL	1.5 diameter	Principal cell	7-14	10	4- 9	7	523.33
5.....	45	♀	4	+	0	14.4	2.4	8.9	1.5	RL	3.5 by 2.4 by 1.0	Transitional oxyphil	8-16	12	6-10	7.5	894.32
6.....	55	♀	2	+	0	....	...	...	...	RU	1.7 by 0.9 by 0.9	Oxyphil	12-16	14	4- 8	6	1,436.02

In some of the tumors the cells were fairly uniform while in others there was a marked variation within the area of a low power microscopic field. This distribution of cells into protean masses, large and small clumps, cordlike structures and alveoli depended to a great extent on the fibrous connective tissue stroma. All tumors examined showed to some extent an irregular increase in fibrous tissue; this was seen as thickened collagenous sheets in some areas and as thin stringy wisps in others. Although all the aforementioned types of cell arrangement are found in normal glands, the change in stroma is a specific attribute of tumors of the parathyroid. The blood vessels of the normal gland, as previously described, are abundant and of a fairly even caliber and distribution while those of the tumor group showed a marked irregularity in caliber and distribution with large, dilated, engorged sinusoidal capillaries being frequently seen.

Castleman and Mallory [1] stressed the significance of the localized character of the proliferative process as being indicative of neoplasia. These authors stated: "The crux of the argument rests, in our opinion, in the localized character of the proliferative process. Our own experience indicates this is frequently limited not merely to one gland but to a portion of a single gland." They further recorded that they had demonstrated a rim of normal parathyroid tissue on one margin of the tumor in 8 of their 19 cases of adenomas and gave seemingly ample reasons for the paucity of such observations by other workers. Though an effort was made to demonstrate normal parathyroid tissue about the tumors described here we were, with the possible exception of case 6, unable to do so.

As noted, the tumor in case 6 differed from the other tumors in several respects, and its diagnosis as an adenoma is only tentative. The histologic feature most indicative of a neoplastic formation was the narrow rim of normal principal cells, but these cells showed no evidence of compression, and it could not be proved that they did not represent a group of cells displaced from the smaller mass of tissue. There is also the possibility that the latter region represented the original gland and the larger one an adenoma, but the presence of morphologically identical abnormal cells in both portions does not substantiate this assumption. Further, the cordlike arrangement of cells, their relative uniformity of size, shape and structure, the comparative lack of cell hypertrophy and nuclear multiplicity and the more nearly normal distribution of fibrous tissue stroma and vascular supply are all somewhat indicative of hyperplasia. The hyperplasias reported by Castleman and Mallory [1] were generalized, involved all the glands and consisted entirely of principal ballooned or *wasserhelle* type cells. The most significant fact against the diagnosis of the condition in case 6 as a hyperplastic gland is that the other glands were not notably abnormal. It is possible, however, that comparison with the thyroid gland may be helpful, for

it is not uncommon to find a lobe or portion of a lobe to be hyperplastic while the remainder of the gland is relatively normal. Though the parathyroid tissue is commonly divided into four glands, it is assumed that the tissue functions as a unit and hence by analogy with the thyroid a focal hyperplasia of the parathyroid tissue may occur, giving rise to an apparent tumor.

Much remains to be learned about the physiology of the parathyroid gland and the significance of its various component cells. Among the unknown details is the factor or factors which bring about the formation of oxyphil cells. As noted, case 6 was one of carcinoma of the breast with multiple bone metastases as well as generalized osteitis fibrosa cystica. In another case of carcinoma of the breast with bone metastases but no roentgenologically identifiable fibrocystic bone changes, most of one of the parathyroids was occupied by a large nest of oxyphils. These cells were in every respect morphologically similar to those in case 6 and contained the only mitotic figure seen in this study. This mass of oxyphils may be interpreted as representing an early stage of a parathyroid tumor or as an oxyphil cell response to bone destruction. In the latter regard it is of interest to note, and speculate on the possible significance of, 2 cases of carcinoma of the breast with secondary osseous lesions in which the parathyroids showed definitely abnormal masses of oxyphil cells. The functional activity of the various cell types has been previously discussed,[4] and it is beyond question that the principal cell forms are the primary and essential endocrinologically active cell types. The discovery of a parathyroid tumor associated with a generalized osteitis fibrosa cystica and consisting almost entirely of oxyphils is definite evidence of the functional activity of this cell. The presence of a mitotic figure within an oxyphil is considered proof that these cells are capable of growth activity and are not merely inert structures. The histologic studies of fat, glycogen and mitochondria are recorded elsewhere [4] and repetition is unnecessary. It is felt that, though admittedly varying in degree, all cells, including the mature oxyphil forms, are capable of elaborating parathyroid hormone.

CRITERIA FOR DIAGNOSIS OF ADENOMA

The detailed study of the tumors described and a review of the literature reveal many interesting points in the diagnosis of parathyroid adenomas, i. e., a benign neoplastic growth of the parathyroid tissue.

No constant cell type is found in these adenomas, and though each tumor consists essentially of one cell form, i. e., principal cells, transitional oxyphil forms or mature oxyphil cells, it is extremely uncommon to find a parathyroid tumor entirely composed of one cell type. Though parathyroid adenomas are classified into several varieties, e. g., transitional oxyphil, there is a tremendous variation in cell size, structure and phase of development from tumor to tumor, area to area, and indeed

within the confines of a single microscopic field. The recognition and correct interpretation of these cell forms require a knowledge of the normal cell and its transitional phases. Cellular and nuclear gigantism are not necessarily present, but these large forms are frequently found. Many cells measure 50 microns in diameter while nuclei 20 microns in diameter are not uncommon. Each cell of an adenoma is, however, usually larger than its normal counterpart, and the average cell is always of greater magnitude. In judging the cell size it is well to remember that the only true criterion is volume.

Multiplicity of nuclei was present in all the cases recorded in this paper. Though this feature is not commonly noted it is felt that a careful search will often, if not always, reveal cells containing from 2 to 6 nuclei. The multiple nuclei are interpreted as indicating amitotic division. Many of the nuclei of the adenoma cells contain from 2 to 5 or 6 large, strongly acidophilic nucleoli.

There is no definite cell arrangement in the parathyroid adenomas. The distribution of cells is somewhat dependent on the location of the fibrous tissue stroma. Thus adenomas are found in which the cells are arranged in protean masses, large and small clumps, cords and acinar structures.

The parathyroid adenomas show a well defined irregularity in amount and distribution of fibrous tissue stroma. In some areas this tissue is abundant and collagenous and in others thin, stringy and barely demonstrable. This stromal change varies in degree in different tumors as well as in different areas within any one adenoma. Similarly there is a well marked variability in the caliber, number and distribution of the sinusoidal capillaries, and these thin-walled delicate structures possess a marked tendency to hemorrhage.

Most adenomas contain very few, if any, fat cells. From the examination of the tumors it is evident that the fat, which is normally present in large quantities in the elderly adult gland, is the first tissue replaced by the tumor growth.

SUMMARY

Six cases of parathyroid tumor are reported. Four of the tumors are diagnosed as transitional oxyphil cell adenoma, one as principal cell adenoma and one as probably oxyphil cell adenoma.

All tumors produced roentgenologically recognizable bone destruction (osteitis fibrosa cystica), but no nephrolithiasis was demonstrable.

Evidence is presented to show that all forms of the parathyroid cell are capable of producing parathyroid hormone.

Several criteria for the diagnosis of parathyroid adenoma are discussed. These are: increased size of the individual cells, multiple nuclei, irregularity of stroma and capillary form, and variability of cellular arrangement.

CYANOTIC ATROPHY OF THE LIVER

A WAX MODEL RECONSTRUCTION

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AND

J. W. DEVEREUX, M.D.

CHICAGO

The changes produced in the liver because of impaired circulation of the blood are well known. Lambert and Allison [1] described several types of lesions produced as a result of chronic passive hyperemia of the liver. These represented different stages in the one process. The cause of the disappearance of the liver cells has been a subject of some discussion. Orth [2] and others attributed the central necrosis of the liver cells to pressure atrophy. Mallory [3] ascribed the necrosis to toxins acting in combination with a poor nutrition of cells. MacCallum [4] suggested that anoxemia is the important factor in central necrosis of cyanotic atrophy of the liver. Gerlach [5] attributed the final disintegration of cells to anoxemia and then to pressure.

The well known gross and histologic pattern produced by venous stasis is dependent on atrophy and destruction of the liver cells in the center of the lobules, with replacement by red and white blood cells mixed with some fragments of liver tissue. In the beginning of the change there is nothing more than hyperemia of the central veins and the surrounding sinusoids. As the circulatory impairment increases, there is atrophy of the liver cells in the center of the lobules and hemorrhage. These changes extend for varying distances from the central vein to the periphery of the lobule. The liver cells are sharply demarcated from this zone of blood.

When the venous stasis becomes very severe, such alterations are increased so as to involve a large portion of the lobule. The destruction

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1. Lambert, R. A., and Allison, B. R.: Bull. Johns Hopkins Hosp. **27**:351, 1916.

2. Orth, J.: Compendium der pathologisch-anatomischen Diagnostik, ed. 6, Berlin, A. Hirschwald, 1900, p. 545.

3. Mallory, F. B.: J. M. Research **9**:455, 1911.

4. MacCallum, W. G.: Textbook of Pathology, Philadelphia, W. B. Saunders Company, 1930, p. 469.

5. Gerlach, W., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1930, vol. 5, pt. 1, p. 91.

of liver tissue does not extend concentrically throughout the lobule. The liver parenchyma in the region of the portal structures remains intact. At certain intervals along the periphery the erythrocytes that have replaced the usual liver parenchyma extend beyond the periphery of the lobule to merge with similar regions of an adjacent lobule or lobules. When this change is marked, the portal triad structures are surrounded by a rim of intact liver parenchyma, and this in turn is encircled by a broad zone of red cells. Because of this alteration, the usual lobule pattern seems reversed, in that gray-brown or yellow tissue appears to be in the center and red tissue at the periphery. This was referred to by Saltykow [6] as the paradoxical appearance of cyanotic atrophy.

Gerlach [5] discussed other phases of the changes in chronic cyanotic atrophy of the liver. He concluded that the irregular distribution of the destroyed liver tissue is due to the pressure exerted on the liver cells from the dilated capillaries, in combination with a pressure similarly exerted by the capsule. He also stated that the liver tissue regenerates when chronic cyanotic atrophy is marked, but not to the extreme degree seen in cirrhosis. As far as we know, there have been no studies of the regions of cyanotic atrophy of the liver in all three of its dimensions.

WAX MODEL RECONSTRUCTION

With this in mind, a wax model reconstruction of regions of destroyed liver cells was made.

The liver used was from the body of a man who died in the Presbyterian Hospital, in the service of Dr. Ernest E. Irons, as a result of coronary thrombosis. The important changes found in his body were: generalized arteriosclerosis, recent and old thrombosis of the right coronary artery, infarction scars of the posterior wall of the left ventricle and posterior half of the ventricular septum and more recent infarct of the ventricular septum. The liver grossly had the usual appearance of rather marked cyanotic atrophy. Histologically, the parenchyma about the central veins was destroyed for varying distances toward the edge of the lobule and was replaced by erythrocytes and occasional leukocytes, while at the periphery were liver cells in varying degrees of compression and necrosis. A piece of liver tissue 11 by 3 by 1.8 mm. was cut serially into one hundred and forty-eight sections. Tracings representing a magnification of 30 were made of every third section. A wax model proportional to the sections was made.

In the stained sections the lobules of the liver were cut in the transverse, longitudinal and oblique planes. The regions of atrophy corresponding to the centers of lobules varied in size. In many places they extended beyond the periphery of the lobule and coalesced with similar regions of adjacent lobules. When this fusion was extensive, small portal triad structures were completely surrounded by intact liver tissue, and this in turn was encircled by a zone of atrophy. Commonly, however, in this liver small portal triads were only partially surrounded by such regions.

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6. Saltykow, S.: Verhandl. d. deutsch. path. Gesellsch. **5**:104, 1902.

The regions of atrophy represented in figure 1 are fair samples of the changes produced in the liver by the venous stasis. The structure labeled *1* represents the portion of a lobule where liver tissue is absent as a result of chronic cyanotic atrophy. Such changes seem to be greatest at the end where the central vein begins, and from here they proceed through the length of the lobule, decreasing slightly in extent. About the periphery are areas labeled *2, 3, 4* and *5,* that represent portions of lobules altered in a manner similar to the changes in *1.* Along contiguous sides the regions of cyanotic atrophy of two lobules labeled

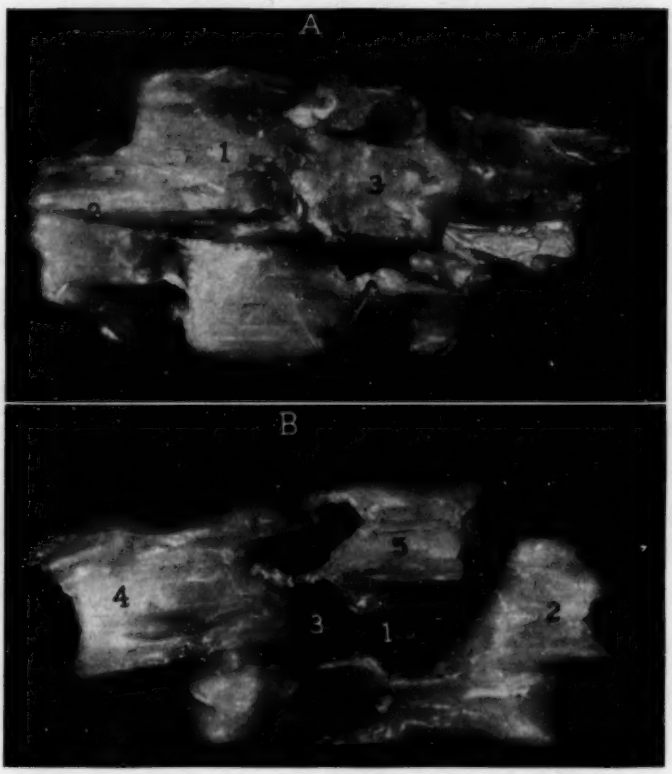

Fig. 1.—Wax model showing regions of destroyed liver cells. In *A* the region labeled *1* represents the place in a single lobule where, from end to end, the liver tissue has disappeared. The base of the lobule is at the top. The numerals *2, 3* and *4* indicate places in adjacent lobules from which the liver tissue has completely disappeared. The hole below *3* and other similar regions in *B* are places where liver tissue and portal vessels were still present when the tracings were made. *B* is the other side of the areas seen in *A*. The numeral *3* in this region represents the periphery of a lobule where liver tissue remained. The other dark spots also are places where liver tissue was present in the sections. The numeral *5* indicates the region from which liver tissue had disappeared altogether in a lobule not shown in *A*.

1 and *2* are fused for almost their entire length. These two lobules happen to have parallel long axes. Along another side region *1* has a smooth periphery, without being joined to other similar places of atrophy. In this instance fairly large portal structures are adjacent and prevent coalescence with nearby lobules. Region *3* represents a portion of a third lobule from which the liver tissue has disappeared, and this lobule is directed slightly obliquely to the lobule numbered *1*. Fusion occurred only where the two came close enough to be in contact.

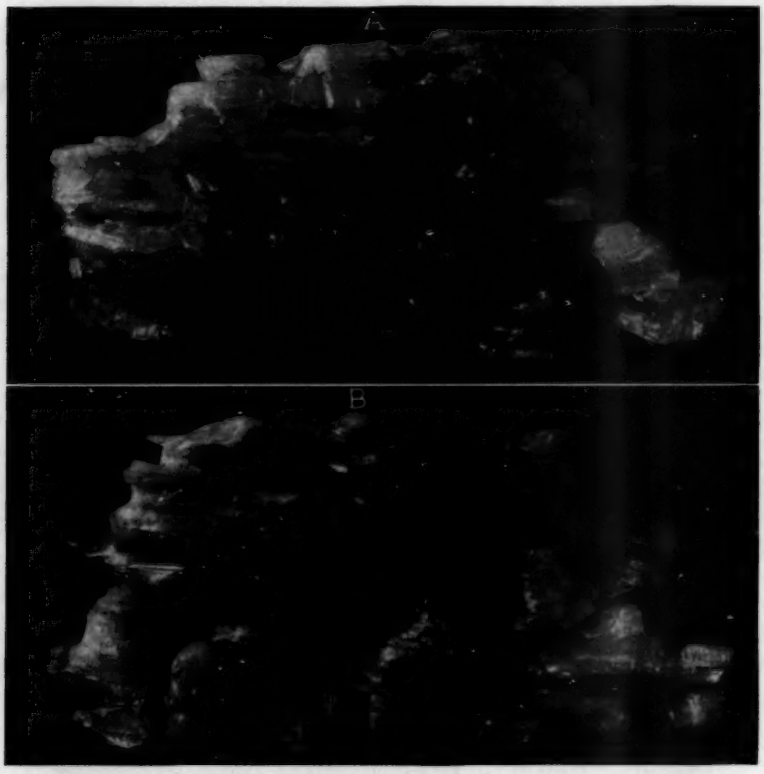

Fig. 2.—Wax model. In *A* the lighter places are regions of cyanotic atrophy from which the liver tissue has practically disappeared. The darker regions represent the peripheries of lobules where the liver cells, portal veins and accompanying vessels are still present. Altogether there are about thirty lobules. *B* is a photograph of the opposite side of the places illustrated in *A*.

Region *4* is directed obliquely to a considerable degree. On account of its position it is coalesced with region *1* only slightly and with region *3* considerably more. Along another portion of the periphery of the atrophic region *1* coalescence also occurred with one more district of atrophy. This was a lobule which is labeled *5*. It is only partly

shown by the model and is also obliquely directed to region *1*. In all, about 30 per cent of the periphery of the area of cyanotic atrophy in lobule *1* is continuous with areas of similar atrophy in altogether four different lobules.

The reader should keep in mind that the actual amount of liver tissue destroyed is represented by the model (fig. 2) and is far more extensive than would be estimated from the examination of single microscopic preparations. The spaces in the model represent areas occupied by intact liver tissue, including portal triad structures. It is apparent that there are many regions where the districts of destroyed liver tissue have coalesced. Some are broad; others, narrow. The extent of the fusion, as has been pointed out, depends on whether the long axes of adjacent lobules are parallel or at an angle to one another. Those that lie parallel are joined for a considerable distance; others that lie obliquely are united for only a short distance. In some regions of the reconstruction there is a more marked destruction of liver tissues than elsewhere. This is in accord with the ideas expressed on the subject by various writers.

In general, a lobule exhibiting changes of chronic cyanotic atrophy may merge at the periphery with four or five adjacent lobules. The degree of the blending is variable, depending on the position of the adjacent lobules. Those that lie parallel are united without interruption for considerable distances by medium-sized bands of fusion in which the process of destruction is continuous from the center of one to the center of the other lobule. Less than 50 per cent of the periphery of a lobule is involved in the regions of fusion. The damming back of venous blood does not extend beyond the periphery of the lobule, where the portal vein and accompanying vessels are located. Portal structures are barriers and prevent regions of cyanotic atrophy from extending through them. The amount of liver tissue destroyed seems to be greatest in the region where the central vein leaves the lobule.

CENTRAL CIRRHOSIS

For a time, some pathologists [7] thought that the changes produced in cyanotic atrophy of the liver led eventually to cardiac or central cirrhosis. In some quarters, the idea still prevails. Letulle [8] discussed the subject and still advocated that the changes produced by chronic passive hyperemia lead to this type of cirrhosis. On the other hand, Gerlach [5] and others denied that there is such a thing as a cardiac or central cirrhosis.

7. Parmentier, E.: Études cliniques et anatomo-pathologiques sur le foie cardiaque, Paris, G. Steinheil, 1890.

8. Letulle, M.: Anatomie pathologique, Paris, Masson & Cie, 1931, vol. 3, p. 1633.

In the late stages of a long continued and marked passive hyperemia the liver may be firmer than usual and shrunken. The capsule and the walls of the hepatic veins have an increased amount of fibrous tissue. The fibrous tissue in the region of the portal triad structures may seem to be increased but this is relative and not actual. Such fibrous tissue is conspicuous because of the marked destruction of liver tissue.[9] In places the fibrous trabeculae projecting into the parenchyma from Glisson's capsule may surround groups of lobules, but these changes are not those of true cirrhosis. The color of livers changed by chronic passive hyperemia is different from the color of cirrhotic livers, and also the granular appearance is more pronounced in the latter. Herxheimer [10] stated that with stains in which silver is used to make the stroma conspicuous he failed to find changes in the liver similar to those seen in cases of true cirrhosis.

Piery [11] explained the fibrous tissue proliferation in livers having the changes of impaired circulation on the basis of an inflammatory process. In this regard, Dr. E. R. LeCount called our attention to a liver which actually had central cirrhosis. It came from the body of a patient who had chronic hyperplastic tuberculous pleuritis, chronic deforming mediastinitis and obliteration and calcification of the pericardium. This case formed the basis of a report by Dr. J. B. Herrick entitled "Pericarditic Pseudo-Cirrhosis of the Liver." [12]

Camera lucida tracings of stained serial sections were made by Dr. Leila Jackson. The tissue was made up of irregular masses of liver cells, limited by conspicuous fibrous tissue that did not conform to the usual lobule pattern. This fibrous tissue was not prominent about the portal vein. In the stroma that subdivided the lobules of the liver the blood vessels were not associated with bile ducts. These vessels were followed from section to section, and their continuity with larger hepatic veins was demonstrated. The liver cells adjacent to the dense fibrous tissue were atrophic, and the sinusoids were distended with erythrocytes. The liver tissue adjacent to the portal triad was healthy. Sketches of some of the tracings made from serial sections are shown in figure 3. Obviously, the lobules of the liver were subdivided by fibrous tissue, and included in this stroma are veins which, when traced, were seen to empty into larger ones. The increase of this fibrous tissue was mostly in the center and not in the periphery of the lobules. Such a change may be called central cirrhosis.

9. Karsner, H. T.: Human Pathology, ed. 2, Philadelphia, J. B. Lippincott Company, 1929, p. 683.

10. Herxheimer, G.: Beitr. z. path. Anat. u. z. allg. Path. **43**:284, 1908.

11. Piery, H.: Lyon méd. **50**:997, 1909.

12. Herrick, J. B.: Tr. Chicago Path. Soc. **5**:71, 1902.

The condition, however, may not be a result of chronic passive hyperemia of the liver. The disease was explained by a retrograde lymphangitis from the tuberculosis of the mediastinum and pleura following along the inferior vena cava and hepatic veins, but without obvious tuberculous granulation tissue, because the tuberculosis was hyperplastic and almost totally devoid of foci of caseation. Such chronic inflammation is common in the peripheries of areas where more pro-

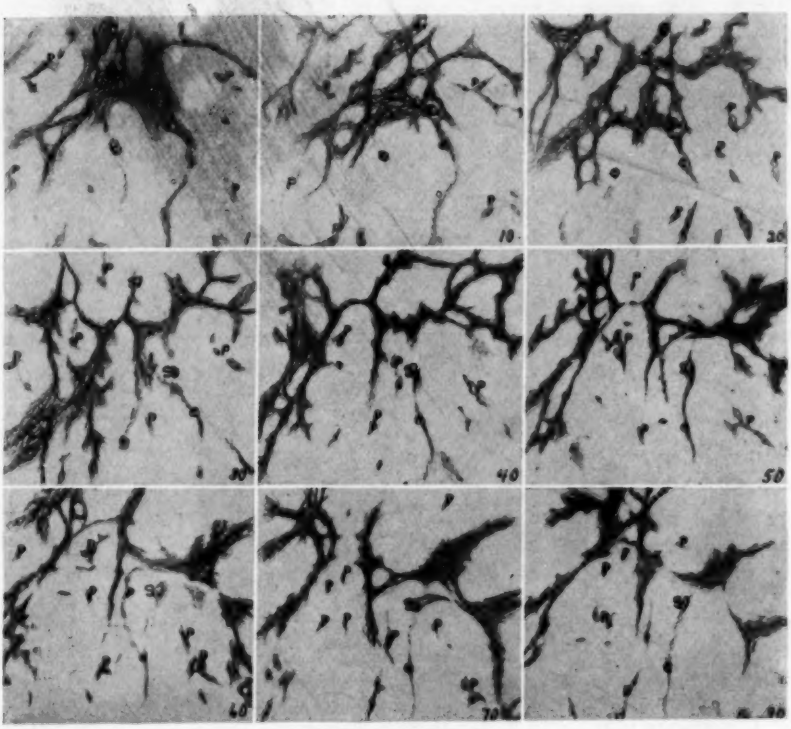

Fig. 3.—Tracings made from serial sections of the liver, indicating the distribution of the fibrous tissue within lobules. *P* denotes the position of the portal structures; *C*, the central veins, and *S*, the sublobular veins.

nounced disease has existed for some time. It is well known that lymphatics from the liver accompany the hepatic veins and ascend into the thorax along the inferior vena cava.[13]

SUMMARY

A wax model reconstruction of the regions of cyanotic atrophy of a liver was made. This method reveals that the amount of liver tissue

13. Delamare, G.: The Lymphatics, Chicago, W. T. Keener & Co., 1904, p. 201.

destroyed is more than it appears to be in stained sections. The regions of atrophy of an individual lobule extend beyond the periphery to coalesce with similar tissues in four or five other lobules, involving less than 50 per cent of the peripheries of such units. Whether the fusion between the regions of cyanotic atrophy of two adjacent lobules is extensive or not depends on the position of these lobules. The fused regions of cyanotic atrophy of adjacent lobules are largest when the latter have parallel axes.

An example of central cirrhosis of the liver is given, and this disease is explained by a retrograde lymphangitis from tuberculosis of the mediastinum and pleura extending along the inferior vena cava.

VITAMIN A DEFICIENCY

IN SPITE OF ADEQUATE DIET IN CONGENITAL ATRESIA OF BILE DUCTS AND JAUNDICE

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The association of severe protracted jaundice with the various manifestations of what is now recognized as vitamin A deficiency was well known to the continental clinicians of the last century. Their reports,[1] while they apparently demonstrated some connection between icterus and hemeralopia, xerosis and keratomalacia, cannot be analyzed critically now because of the omission of any reference to the diets the patients were receiving. It is well known that patients with hepatic disease usually experience anorexia and frequently nausea, vomiting or diarrhea as well. The occurrence of vitamin A deficiency in the cases reported in the earlier literature may have been due to malnutrition associated with these gastro-intestinal disturbances.

For a period of about twenty years in the early part of the present century no additional reports of cases appeared. There was, however,

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1. Bamberger, H.: Krankheiten des chylopoetischen Systems, in Virchow, R.: Handbuch der speziellen Pathologie und Therapie, Stuttgart, Ferdinand Enke, 1855, vol. 6, pt. 1, p. 522. Junge, E.: Verhandl. d. phys.-med. Gesellsch. in Würzburg **9**:219, 1859. Frerichs, F. T.: Klinik der Leberkrankheiten, Braunschweig, F. Viewig & Sohn, 1858, vol. 1, p. 116. Murchison, Charles: Clinical Lectures on Diseases of the Liver, Jaundice and Abdominal Dropsy, New York, William Wood & Company, 1868, p. 372. Fumagalli, A.: Ann. di ottal. e clin. ocul. **2**:471, 1873. Kohn: Rec. d'opht. **1**:185, 1874. Straus, I.: Des ictères chroniques, Paris, J.-B. Baillière & fils, 1878, p. 104. Gorecki, X.: Praticien **3**:427, 1880. Mouly, P.: Contribution à l'étude de l'héméralopie dans les affections hépatiques, Thèse de Paris, no. 217, 1881. Parinaud: Arch. gén. de méd. **7**:403, 1881. Raymond: Praticien **4**:497, 1881. Cornillon, J.: Progrès méd. **9**:157, 1881; **10**:439, 1882. Weiss: Mitth. a. d. ophth. Klin., Tübingen **3**:89, 1882. Leber, T.: Arch. f. Ophth. **29**:224, 1883. Hirschberg, J.: Berl. klin. Wchnschr. **22**:364, 1885. Vincent, G.: L'oeil et le foie, Thèse de Lyon, 1892. Moauro: Ann. di ottal. e clin. ocul. **26**:554, 1893. Baas, K. L.: Arch. f. Ophth. **40**:212, 1894; München. med. Wchnschr. **41**:629, 1894. Thompson, J. T.: Brit. M. J. **2**:597, 1894. Hori: Arch. f. Augenh. **31**:393, 1895. Levi, L.: Presse méd. **4**:165, 1896. Elschnig, A.: Wien. med. Wchnschr. **49**:842, 1899. Purtscher: Arch. f. Ophth. **1**:83, 1900. Volbracht, F.: Ztschr. f. Heilk. **24**:359, 1903. Spassky: Russk. vrach **4**:693, 1906. Groenouw, A., in von Graefe, A., and Saemisch, T.: Handbuch der gesamten Augenheilkunde, ed. 2, Leipzig, Wilhelm Engelmann, 1906, vol. 11, pt. 1, p. 83.

an increase of interest in the subject with the appearance of the publications of Wright [2] and Wagner.[3] In these, as in the older reports, there was no definite information as to the adequacy of the dietary regimen of the patients.

That there is a specific connection between hepatic disease with icterus and vitamin A deficiency became apparent when Blegvad [4] in 1923 and Bloch [5] in 1924 called attention to the signs and symptoms of this deficiency in three patients who were receiving diets rich in vitamin A. Blegvad's patient experienced relief of the symptoms of deficiency only after the intramuscular administration of a cod liver oil concentrate. The patient described by Bloch who recovered spontaneously did so only after the subsidence of the icterus. Owen and Hennessey [6] and Blackfan and Wolbach [7] reported additional instances of vitamin A deficiency with severe jaundice in patients receiving adequate amounts of vitamin A. All these authors considered the vitamin A deficiency to be secondary to defects in the absorption of fat associated with jaundice.

Severe jaundice with complete, or almost complete, exclusion of bile from the small intestine was common to all the cases reported in the literature. Marked enlargement of the spleen and liver was noted in most instances. The patients with this syndrome were described as having Hanot's cirrhosis, hypertrophic cirrhosis of the liver with icterus gravis or biliary cirrhosis. A few cases of a high grade of obstructive jaundice due to malignancy or to cholelithiasis with secondary suppurative or cirrhotic changes in the liver are also found among those reported. In all instances in which it was possible to determine the time relationship between the onset of the jaundice and the appearance of the symptoms of deficiency, it was apparent that jaundice always came first. The interval before the appearance of the symptoms of deficiency varied from weeks to months in children and from months to years in adults.

In recent years Wolbach and Howe [8] have defined the essential pathologic picture in cases of vitamin A deficiency; other observers [9]

2. Wright, R. E.: Statistical and Professional Report of the Government Ophthalmic Hospital, Madras, 1921-1922; Brit. J. Ophth. **6**:164, 1922; Lancet **1**:800, 1931.

3. Wagner, R.: Wien. med. Wchnschr. **74**:1108, 1924.

4. Blegvad, O.: Ugesk. f. læger **85**:942, 1923.

5. Bloch, C. E.: Am. J. Dis. Child. **28**:659 (Dec.) 1924.

6. Owen, H. B., and Hennessey, R. S. F.: Tr. Roy. Soc. Trop. Med. & Hyg. **25**:367, 1932.

7. Blackfan, K. D., and Wolbach, S. B.: J. Pediat. **3**:679, 1933.

8. (*a*) Wolbach, S. B., and Howe, P. R.: J. Exper. Med. **42**:753, 1925; (*b*) **57**:511, 1933; (*c*) Arch. Path. **5**:239, 1928.

9. Goldblatt, H., and Benischek, M.: J. Exper. Med. **46**:699, 1927. Tilden, E. B., and Miller, E. G.: J. Nutrition **3**:121, 1930. Wolfe, J. M., and Salter, H. P.: ibid. **4**:185, 1931. Thatcher, H. S., and Sure, B.: Arch. Path. **13**:756, 1932.

have corroborated these observations in animals. Wilson and DuBois [10] described a similar lesion in children. The structural effects of vitamin A deficiency are characterized by atrophy of the epithelium of various organs and replacement with a stratified keratinizing epithelium, the metaplastic cells arising in foci deep in the epithelium close to the basement membrane. The formation of the keratinizing epithelium begins simultaneously in many foci. The first change that is demonstrable is the appearance of clusters of cells containing large pale nuclei surrounded by deeply basophilic cytoplasm. These cells increase by mitotic division and soon commence to show keratinizing changes. As they increase in size, the clusters of cells undermine the preexisting epithelium. There is also some extension into the supporting tissues. The keratinizing epithelium which replaces the atrophic normal epithelium in the various organs is identical in all locations. In infants the earliest appearance of keratinizing metaplasia is in the trachea and bronchi. The epithelium of the renal pelves is usually next involved. The salivary glands, pancreas, uterus, thymus, esophagus, glands of the nasopharynx, bladder, prostate, seminal vesicles and para-ocular glands may also show typical changes. Keratotic changes in the cornea appear late in the disease; far advanced metaplasia may be present in various internal organs with no discernible abnormality in the cornea.

The present article is based on a postmortem study of eleven infants with congenital atresia of the bile ducts. All of them had received diets adequate in vitamin A, and none presented clinical evidence of xerosis or keratomalacia during life.

Microscopic changes diagnostic of vitamin A deficiency, as defined by Wolbach and Howe,[8] were observed in six of the eleven infants, and the clinical histories and autopsy observations in these six cases are presented. In each of these cases the family history was irrelevant.

REPORT OF CASES

Case 1.—An 8 month old white boy was admitted to the hospital on Aug. 13, 1931, because of jaundice. Delivery was normal. Jaundice was noted at birth, with white stools and brown urine, and grew steadily worse. Two weeks before admission anorexia developed, and the infant commenced to lose weight. In a week he became dyspneic. He was breast fed during the first month of life and thereafter was given formulas with added fruit juices, vegetables and cod liver oil for several months.

The infant was fairly well developed, poorly nourished, dyspneic and markedly icteric, with edema of the eyelids. A rachitic rosary was noted. The abdomen was markedly distended, with prominent superficial veins. The liver was felt as a hard nodular mass 4 cm. below the costal edge. The spleen was palpable in the left flank as a mass the size of an orange. There was shifting dulness in the flanks.

10. Wilson, J. R., and DuBois, R. O.: Am. J. Dis. Child. **26**:431, 1923.

The icteric index was 325, with a quantitative van den Bergh reaction of 77. A direct van den Bergh reaction was obtained.

An exploratory laparotomy was made on the third day after admission and revealed marked ascites, splenomegaly, hepatomegaly and atresia of the bile ducts. The infant died the next day.

At autopsy, five and one-half hours post mortem, the liver was enlarged, weighing 287 Gm., firm and dark green. The surface was extremely nodular and cirrhotic. The capsule was thickened. Cut surfaces showed strands of connective tissue running throughout the organ, most prominent in the portal areas. There was marked biliary stasis. The gallbladder was represented by a small tab of fibrous tissue lying in the gallbladder fossa. A fine lumen was present in it. No cystic or common bile duct was demonstrable. The spleen was markedly enlarged, weighing 117 Gm., and was fairly firm. Many subcapsular petechial hemorrhages and a slight increase in fibrous tissue were noted.

In addition, intense generalized icterus, slight edema of the lower eyelids, a recent right rectus incision, 75 cc. of bloody fluid in the abdomen, numerous petechial hemorrhages in the pericardium, dependent bronchopneumonia of both lungs and marked rachitic changes in the long bones and ribs were noted.

The observations on which the diagnosis of vitamin A deficiency was made were as follows: There was marked metaplasia of the epithelium of the trachea with complete replacement of the pseudostratified epithelium by stratified squamous cells. Slight keratinization of this epithelium was observed. The epithelium of the renal pelves showed moderate metaplasia and slight keratinization. There were early metaplastic changes in the pancreatic ducts represented by foci of squamous cells undermining the normal epithelium. The rest of the microscopic examination confirmed the macroscopic observations.

Comment.—The child presented microscopic changes in the trachea, renal pelves and pancreatic ducts indicative of the presence of a moderate degree of vitamin A deficiency in spite of the fact that an adequate diet plus cod liver oil had been received.

Case 2.[11]—A white girl aged 5 months was admitted on Dec. 31, 1931, because of jaundice. Delivery was normal. Clay-colored stools and dark brown urine were observed three days after birth. Icterus was first noted when the infant was 3 weeks old and increased steadily thereafter. The child was breast fed for two weeks and then was given various formulas containing milk, dextrimaltose with vitamin B and water, all of which were taken well. The infant received 1 teaspoonful of orange juice daily and 5 drops of viosterol twice daily, beginning at the age of 1 month. About a month before admission the infant's left ear commenced to discharge and continued to do so for about a week. Several days before admission she appeared to be feverish and vomited several times.

Examination on admission revealed a deeply icteric, poorly developed and poorly nourished infant. She was entirely normal except that the liver was felt as a hard mass 2½ fingerbreadths below the left costal margin. The stool was clay-colored.

The icteric index was 125 and 180, respectively, on two occasions. The van den Bergh reaction was direct. The quantitative van den Bergh reaction was 50 and 36, respectively, on two occasions.

11. This is case 11 of the series reported by Blackfan and Wolbach.[7]

The patient was given a diet of fat-free milk with 50 per cent Karo. She also received orange juice. One grain (0.065 Gm.) of oxgall was given three times a day. The day after admission the temperature rose to 103 F. The next day, after both ear drums were lanced, the temperature returned to normal. The following week a similar series of events occurred. On Jan. 12, 1923, an exploratory laparotomy was performed. No gallbladder or extrahepatic ducts were demonstrable. The infant was still receiving fat-free milk and oxgall. On the seventh postoperative day the wound separated and was resutured. Death occurred three days later, the infant being 6 months old.

At autopsy, sixteen hours post mortem, the liver was increased in size, weighing 240 Gm., was much firmer than normal and was dark green. The surface was finely nodular, and the capsule appeared thickened. Cut surfaces showed pronounced biliary stasis and irregular scarring, the latter being especially marked in the portal areas. Deep in the gallbladder fossa a small sac, 1 cm. in diameter, which contained dark green inspissated bile, was noted. It continued upward toward the liver as a slightly dilated hepatic duct. No ducts were demonstrable below the sac passing toward the duodenum. The ampulla of Vater, while patent toward the pancreas, had no demonstrable connection with the liver. The spleen was enlarged, weighing 30 Gm., and was abnormally firm. Cut surfaces showed an increase in the amount of fibrous tissue.

The other macroscopic observations included a recent right rectus incision; 30 cc. of bloody amber fluid in the abdomen; fibrinous peritonitis; adhesions between the omentum, the body wall and the gallbladder fossa; small adhesions between several loops of bowel and the operative wound; dependent bronchopneumonia of both lungs and marked generalized icterus.

The diagnosis of vitamin A deficiency was based on the fact that the Hassall corpuscles of the thymus were greatly enlarged and were lined by keratinizing squamous cells. The pseudostratified tracheal epithelium showed marked metaplastic changes, having been converted into stratified squamous epithelium. The epithelium of the renal pelves also presented striking metaplasia. The normal transitional epithelium had been converted into thickened keratinizing stratified squamous epithelium. The underlying connective tissue showed acute and chronic inflammatory cellular infiltration. The epithelium of the esophagus was thickened and hyperkeratotic, and the ducts of its glands showed marked metaplasia of the lining cells.

The other microscopic observations confirmed the macroscopic diagnosis. There were, in addition, acute splenitis; a small blood cyst on the mitral valve; mesenteric lymphadenitis; hemorrhages in the lungs, spleen and parathyroid glands, and evidence of rickets and possibly of early scorbutus.

Comment.—This 6 month old infant showed evidence of marked vitamin A deficiency post mortem, but at no time was there any clinical evidence of it. She had received an adequate diet until a short time before death. The fact that she received a diet of fat-free milk for a period of several weeks before death may account in part for the severity of the changes due to the avitaminosis. The possible effect of the oral administration of oxgall in this case cannot be estimated.

Case 3.—A white girl aged 5 weeks was admitted on July 6, 1932, because of jaundice.

There had been difficult instrumental delivery. Jaundice was noted three days after birth and had persisted. The stools were always clay-colored. She was nursed for two weeks and was then given a formula. She took nourishment well and gained weight until a week before admission, when the weight began to decrease.

Examination revealed a fairly well nourished, deeply icteric infant. She appeared to be normal except that the liver was palpable 2½ fingerbreadths below the costal margin.

The stool contained no bile. A direct serum van den Bergh reaction was obtained. The quantitative van den Bergh reaction was 55, and the icteric index, 325.

The infant was given a mixture of whole milk, 50 per cent, Karo and water. She also received 10 drops of haliver oil daily. On July 30, exploratory laparotomy revealed the absence of the extrahepatic biliary passages and atrophy and fibrosis of the gallbladder. The infant recovered quickly and was discharged on August 10. While at home she was given the same diet that she had had in the hospital. She took her feedings well and gained weight for about one month. After that she failed to gain, probably because of a diminution in appetite. The jaundice, with the clay-colored stools and dark urine, continued, and she was readmitted on November 25 because of rapid swelling of the abdomen during the preceding three days.

Examination showed that the abdomen was markedly distended, with dilated superficial veins, shifting dulness and a fluid wave.

A second laparotomy was performed on November 29. No bile duct could be demonstrated. The patient died the next day, at the age of 6 months.

Autopsy, six hours post mortem, showed that the liver was enlarged, weighing 352 Gm. It was firm and greenish gray. On its surface were fine nodules from 2 to 4 mm. in diameter. Cut surfaces showed marked dilatation of the biliary passages. The markings were distorted. The gallbladder was represented by a thin plaque of fibrous tissue in the gallbladder fossa. The duodenum was adherent to the fibrous tissue on the under side of the liver. No common bile duct was demonstrable. The transverse colon and several loops of jejunum were bound down to the hilus of the liver with dense fibrous adhesions. The spleen was enlarged, weighing 50 Gm., and had a somewhat irregular surface. Intense generalized icterus, slight edema of the eyelids, a small amount of orange fluid in the peritoneal cavity, a recent right rectus incision and patchy atelectasis in both lungs were also noted.

The features diagnostic of vitamin A deficiency were the early metaplastic changes in the epithelium of the renal pelves. In some areas there were foci of stratified squamous cells undermining the normal lining cells. The rest of the microscopic examination confirmed the macroscopic observations and revealed, in addition, a moderate amount of diffuse hemorrhage into the alveoli of the lungs with a small amount of inflammatory exudate in some areas, congestion and edema of the lungs, acute splenitis and early rachitic changes in the long bones.

Comment.—This 6 month old infant showed slight early changes indicative of vitamin A deficiency in spite of having received an adequate diet plus haliver oil.

Case 4.—A white girl aged 8 weeks was admitted on Oct. 25, 1932, because of jaundice. The infant's mother had been well until the middle of the seventh month of pregnancy, when symptoms of toxemia developed. She was taken to

the hospital two weeks later, and labor was induced. The infant was one of twins, weighing only 5 pounds and 1 ounce (2,300 Gm.) at birth. She nursed well and received, in addition, complementary feedings of whole milk, Karo and water. She gained as rapidly as did her normal twin. However, jaundice was observed in the infant at birth and persisted until the time of admission. The stools were clay-colored, and the urine was dark brown at all times.

She appeared to be a poorly developed but well nourished, jaundiced infant. The liver was felt 2 fingerbreadths below the costal margin, and the spleen was just barely palpable.

The icteric index was 100.

Exploratory laparotomy was performed on November 18, and a fibrosed atrophic gallbladder was observed. The cystic and common ducts could not be demonstrated. Following the operation the temperature soon fell to normal, remaining at that level for several days, after which it rose again. In addition to her diet the patient received 8 grains (0.52 Gm.) of oxgall daily. She nursed well but vomited occasionally. The icteric index persisted at 100. Several days before death cough, dyspnea and signs of pneumonia developed. She died on December 10, at the age of 12 weeks.

At autopsy, seven hours post mortem, the liver was normal in size but fairly firm and presented a finely nodular surface. The right lobe was adherent to the anterior abdominal wall; while the stomach, duodenum, ascending colon and hepatic flexure were adherent to the hilar region. The capsule of the liver was slightly thickened. Cut surfaces showed increased fibrous tissue about the lobules of the liver, the latter appearing diminished in size. The gallbladder was represented by a fibrous, elongated, lumenless structure. No external biliary ducts were demonstrable. The spleen was of normal size. There was marked generalized icterus, and numerous small scattered areas of atelectasis were present in the lungs.

The evidences of vitamin A deficiency revealed by microscopic examination of the tissue were as follows: The renal pelves showed from slight to moderate metaplastic changes in the epithelium with early keratinization of the lining cells. The pancreatic ducts also showed some undermining of the epithelium by metaplastic cells.

The rest of the microscopic examination confirmed the macroscopic observations and revealed, in addition, bronchitis, bronchopneumonia, hypoplasia of the bone marrow, petechial hemorrhages and hemosiderosis of the spleen and early rickets.

Comment.—This 12 week old infant showed slight evidence of vitamin A deficiency post mortem in spite of having received an adequate diet. It is of interest that, in spite of the icterus, her growth and development had paralleled that of her normal twin. Factors that possibly were responsible for the early development of vitamin A deficiency in this case were the toxemia of the mother, the prematurity of the infant and the fact that she was one of twins and therefore puny. The febrile postoperative period, which lasted for several weeks, may also have been responsible in part. It is not possible to estimate the effect of the administration of oxgall in this case.

Case 5.—A Jewish boy aged 4 months was admitted on Jan. 17, 1933, because of jaundice. He had otitis media six weeks before admission. Jaundice was

noted three days after birth and became progressively worse. White stools and dark brown urine were noted from the first. The infant was breast fed and received, in addition, complementary feedings of a mixture of milk, water and dextrimaltose. He had vomited a good deal but grew and developed normally. When he was 6 weeks old, enlargement of the liver was noted. When he was 3 months old, this was again observed by a physician, who prescribed a preparation of oxgall and increased the feedings.

Examination revealed a well developed, well nourished, deeply jaundiced infant. He was apparently normal except that the skin bore several furuncles, and the liver was enlarged so as to reach half-way to the iliac crest. The stools were grayish white.

The icteric index varied between 75 and 200. The van den Bergh reaction was diphasic.

The patient was given a transfusion of 125 cc. of citrated blood shortly after admission. Following that the icteric index rose from its initial level of 75 to 225. He was given fat-free milk, orange juice and water, all of which he took well. Beginning January 26 he was also given 6 grains (0.4 Gm.) of calcium glucoside and 20 drops of haliver oil daily. The temperature was normal until after the transfusion, when it rose to 103 F., falling irregularly to 100 F. after four days. At that time he showed signs of bronchitis. The temperature fluctuated between 97 and 99.5 F. thereafter.

On February 1 an exploratory laparotomy was performed, and the gallbladder was observed to connect normally with the duodenum. The gallbladder did not contain bile. The jaundice, with dark urine and clay-colored stools, persisted, but the infant took nourishment well and did not vomit. On February 4 the wound ruptured and was resutured, following which a cough, râles in the chest and a temperature of from 102 to 103 F. developed. Nevertheless the infant ate well and the cough and fever soon subsided. The wound healed, and he slowly gained weight. On March 21 laparotomy was again performed. No hepatic duct was demonstrated. The gallbladder was removed. There was only a slight post-operative reaction, and the infant's progress was good for a time. He ate well and gained weight slowly. However, on March 7 the jaundice became more severe, the abdomen became distended, and edema of the legs appeared. On March 14 1,300 cc. of ascitic fluid was removed. From that time on the infant's condition became worse, and he died on March 23, at the age of 7 months.

At autopsy, ten and one-half hours post mortem, the liver was somewhat enlarged and firm. The surface was finely nodular, the nodules measuring from 1 to 2 mm. in diameter. The capsule was thin. The under surface of the liver was adherent to the duodenum and the hepatic flexure, and the liver was a dark mottled green, the mottling being due to an increased amount of perilobular connective tissue. There was marked biliary stasis, the bile ducts appearing prominently. The gallbladder was not demonstrable. The common bile duct was present and admitted a fine probe. No left hepatic duct was demonstrable. The right hepatic duct existed as a fibrous cord, 11 mm. long. The common duct was patent into the duodenum but had no connection with the liver. The spleen was larger and firmer than normal, and cut surfaces showed accentuation of the fibrous markings. An accessory spleen, 14 by 12 by 8 mm., was present at the hilus. It, too, showed an increased prominence of fibrous tissue.

Marked generalized icterus; recently healed scars resulting from a right rectus incision; 75 cc. of clear amber fluid in the abdomen; dense adhesions involving the upper portion of the ileum, jejunum, hepatic flexure, round ligament of the liver

and omentum; edema and congestion of the mucosa of the gastro-intestinal tract, and congestion of the kidneys were noted. The thoracic organs were not examined.

The diagnosis of vitamin A deficiency was based on the moderate metaplastic changes observed in the epithelium of the renal pelves. There was complete replacement of the normal epithelium by stratified squamous cells in some areas and only undermining of the normal epithelium by foci of metaplastic cells in others.

The rest of the microscopic examination confirmed the macroscopic observations and revealed, in addition, fatty changes in the renal tubules and acute splenitis.

Comment.—This 7 month old infant showed evidence of a moderate degree of vitamin A deficiency in spite of having received an adequate diet plus haliver oil.

Case 6.—A 6 month old white girl was admitted on March 8, 1934, because of jaundice, which was noted at birth and was of unvarying intensity thereafter. The stools were clay-colored and sometimes streaked with blood. The urine was always dark orange. There was frequent vomiting of recently eaten food during the first three months of life but none after that. A slight cough was noted occasionally. The infant was breast fed for one month and was then given a mixture of whole milk, water and Karo. She refused cod liver oil and orange juice. There was little gain in weight after the first few weeks of life.

Examination revealed a fairly well developed, poorly nourished, icteric infant with a large, firm liver and a palpable spleen.

The stool revealed an absence of bile and the presence of occult blood. The icteric index was 60. The van den Bergh reaction was direct; quantitatively it was 2.35 units.

The patient was given a mixture of 2 per cent milk, 50 per cent dextrose and water and also received 2 ounces (60 cc.) of orange juice and 10 drops of haliver oil daily. She took these feedings well. On March 17 she was operated on and died on the operating table.

At autopsy, two hours post mortem, the liver appeared smaller than normal and was dark green. The surface was rough and finely nodular. Cut surfaces presented an increased amount of peripoıtal connective tissue. A strand of connective tissue representing an atrophic gallbladder was observed in the fossa of the gallbladder. No common or cystic ducts could be demonstrated. The spleen was enlarged, weighing 75 Gm. Its capsule presented several patches of thickening anteriorly.

Bilateral craniotabes, rachitic changes in the ribs and long bones, a recent right rectus incision, marked generalized icterus, a few cubic centimeters of icteric fluid in each pleural cavity, some hypertrophy of the right ventricle of the heart, a moderate amount of emphysema of the lungs, marked edema of the mucosa of the stomach and a few small acute ulcers in the ileum were noted.

The microscopic observation on which the diagnosis of vitamin A deficiency was made was the presence of a slight or moderate amount of metaplastic keratinizing epithelium undermining the normal lining cells of the renal pelves.

The rest of the microscopic examination confirmed the macroscopic observations and revealed, in addition, slight early bronchopneumonia.

Comment.—This 6 month old infant showed evidence of a slight degree of vitamin A deficiency in spite of having received an adequate diet.

OBSERVATIONS

Postmortem studies of eleven infants with congenital atresia of the bile ducts were made. Although these infants had received an adequate diet and, in some instances, vitamin A in some form in addition, microscopic examination demonstrated vitamin A deficiency in six of them. All but one of the infants who showed evidence of the avitaminosis were 6 months of age or older. The one exception was a premature infant whose mother showed symptoms of toxemia before delivery. The infants in whom no histologic evidence of the vitamin deficiency was found were 6 months old or younger (table).

Vitamin A Deficiency in Cases of Congenital Atresia of the Bile Ducts

Severity of Vitamin A Deficiency	Age of Infant	Case
Marked	6 months	2
Moderate	8 months	1
Moderate	7 months	5
Slight	6 months	6
Slight	12 weeks	4
Very slight	6 months	3
None	5 weeks	
None	6 weeks	
None	8 weeks	
None	9 weeks	
None	6 months	

COMMENT

As long ago as 1857, Althof and Müller [12] described the appearance of keratomalacia in two dogs with biliary fistulas which were kept alive for four years. Dolganóff [13] in 1897 tied off the common ducts in dogs and noted the appearance of the ocular signs of what is now recognized as vitamin A deficiency.

The manner in which obstructive jaundice acts to make vitamin A unavailable to the body is only partially understood. Blegvad's [4] experience with his patient who responded to the intramuscular administration of a special extract of cod liver oil but not to the oral administration of the oil led him to express the belief that the absence of bile from the small intestine in cases of severe obstructive jaundice in some way prevents the absorption of the fat-soluble vitamin A.

12. Althof, H., and Müller, H.: Würzb. med. Ztschr. **2**:349, 1861.

13. Dolganoff, W.: Arch. f. Augenh. **34**:196, 1897.

More recently Schmidt and his co-workers [14] have shown that dogs with an induced vitamin A deficiency and exclusion of bile from the small intestine, due either to obstruction of the common duct or to formation of fistulas between the gallbladder and the colon, could not be cured of disease due to vitamin A deficiency with cod liver oil or carotene given orally. The signs of the deficiency in these animals could, however, be made to disappear following the intramuscular administration of vitamin A. Similar results were obtained by these investigators by giving carotene or cod liver oil by mouth together with bile salts.

However, it is not certain that the failure of icteric patients to absorb vitamin A is related directly to the faulty absorption of fat which occurs in jaundice, since neither vitamin A nor its precursor, B-carotene, is a fat; the former is an alcohol [15] and the latter a hydrocarbon.[16] Both are readily separated from the fats with which they are found by the process of saponification, carotene and vitamin A remaining in the unsaponified fraction. The part played by bile in the absorption of complex hydrocarbons and their alcohols has not yet been elucidated. It has been shown,[17] however, that both bile and certain pancreatic enzymes are necessary for the absorption of cholesterol, a substance chemically allied to vitamin A and carotene. The absorption of cholesterol and the absorption of fat are, however, entirely independent of each other; [17] it may well be that the same is true of the absorption of fat and of vitamin A.

Some degree of vitamin A deficiency is probably much more common in patients with severe protracted jaundice than is now generally recognized. Wolbach [18] showed that the ocular changes, i. e., xerosis and keratomalacia, are among the last to appear in patients and animals with vitamin A deficiency. The six patients here described showed definite histologic evidence of avitaminosis, although they were clinically without signs or symptoms of it.

Although this study was made entirely on infants, it is reasonable to assume that the conclusions that are drawn from it are applicable to adults as well. There is no reason to suppose that the mechanism of absorption of vitamin A in children is different from that in adults. Moreover, the literature contains reports of cases of adults [19] with severe protracted jaundice in whom vitamin A deficiency developed in spite of the fact that they received definitely adequate diets.

14. Schmidt, W., and Schmidt, C. L. A.: Univ. California Publ. Physiol. **7**:211, 1930. Greaves, J. D., and Schmidt, C. L. A.: J. Biol. Chem. **105**:xxxi, 1934.

15. Karrer, P.; Morf, R., and Schopp, K.: Helvet. chim. acta **14**:1431, 1931.

16. Karrer, P.; Helfenstein, A.; Wehrli, H., and Wettstein, A.: Helvet. chim. acta **13**:1084, 1930.

17. Mueller, J. H.: J. Biol. Chem. **27**:463, 1916.

18. Blackfan and Wolbach.[7] Wolbach and Howe.[8a, c]

19. Blegvad.[4] Owen and Hennessey.[6]

SUMMARY

Microscopic evidence of vitamin A deficiency was found in six of eleven infants with severe protracted jaundice due to congenital atresia of the bile ducts in spite of the fact that they were receiving diets adequate in vitamin A. The deficiency occurred in five of the six infants who lived at least six months. The sixth infant to show evidence of avitaminosis was a premature twin infant.

The presence of this deficiency disease may be overlooked because the specific ocular changes of vitamin A deficiency occur late in the course of the disease.

The deficiency apparently occurs as a result of failure of absorption of vitamin A from the gastro-intestinal tract due to the absence of bile.

There is evidence indicating that the parenteral administration of vitamin A is effective in patients in whom vitamin A deficiency develops as a result of severe obstructive jaundice. The oral administration of the vitamin together with bile salts also is possibly of value.

SUSCEPTIBILITY TO DENTAL CARIES IN THE RAT

VI. INFLUENCE OF ORANGE JUICE AND THE ACID-BASE BALANCE OF THE DIET

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Several theories of the etiology of dental caries are based on the assumption that susceptibility to the disease depends on or is influenced by a disturbance of the acid-base balance of the body reflected as augmented acidity or impaired neutralizing power either of the saliva or of the tooth "fluids." Among those who have advanced views of this kind are Broderick,[1] Bödecker,[2] Jones, Larsen and Pritchard,[3] Kugelmass and King[4] and Grove and Grove.[5] The views of these authors coincide on some points and diverge widely on others, and the evidence adduced, based on studies of human material, is no more than suggestive. Yet a degree of general acceptance has been gained by the view, particularly, that the ash reaction of the diet may be a factor of importance in dental caries, and from the experimental point of view certain scattered observations have made it desirable to submit the question to study. Mellanby and Pattison[6] have reported that cereals, which are acid-forming foods, may be caries-promoting agents in the human dietary; these workers do not, however, interpret this observation as supporting the acid-base theory. Hanke[7] has stressed the value of

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1. Broderick, F. W.: Dental Medicine, St. Louis, C. V. Mosby Company, 1928.

2. Bödecker, C. F.: Dental Cosmos **71**:586, 1929.

3. Jones, M. R.; Larsen, N. P., and Pritchard, G. P.: Dental Cosmos **72**:439, 574, 685 and 797, 1930.

4. Kugelmass, I. N., and King, T. B.: Arch. Pediat. **50**:307, 1933.

5. Grove, C. J., and Grove, C. T.: Dental Cosmos **76**:1029, 1934.

6. Mellanby, M., and Pattison, C. L.: Brit. M. J. **1**:507, 1932.

7. Hanke, M. T.: Diet and Dental Health, Chicago, University of Chicago Press, 1933.

large doses of orange and lemon juice in combating dental caries in children, and, although these authors also incline to a different interpretation, their findings may be regarded as favoring the views under discussion since citrus fruit juices in large amounts shift the dietary ash reaction toward alkalinity. Of immediate interest to ourselves has been the fact that the methods we have used for the production and study of experimental dental caries in rats (Rosebury, Karshan and Foley [8]) involve the feeding of diets containing as the major constituent cereals—rice or corn. We have shown that chemically identical diets which were physically altered by grinding the cereal to a fine powder are entirely without caries-producing effect, but the important question remains whether caries can be produced experimentally by means of a diet with an alkaline ash.

EXPERIMENTS

The influence of an alkaline dietary ash on the production of experimental dental caries in rats was studied by two methods, one of which also involved a direct test in the rat of the observations of Hanke that citrus fruit juices fed in large quantities are effective against caries in children. At the same time, in the expectation of a reduction of experimental caries as a result of the feeding of citrus juice, two additional control groups were instituted in order to assist the analysis of such a finding. The diets employed are described in table 1.

TABLE 1.—*Diets Used in Experimental Study of the Production of Caries*

Component	Percentage of Component in Given Diet					
	73	74	75	76	77	78
Brown rice, 10 mesh	92	92	92	92	..	69
Dried lima beans, 10 mesh	..	..	..	..	92	23
White potato dextrin	8	8	8	8	8	8
Orange and lemon juice	Ad lib.	..	..	..	..	..
Synthetic citrate mixture 1	..	Ad lib.	..	..	..	..
Synthetic citrate mixture 2	..	..	Ad lib.	..	..	..
Water	..	..	..	Ad lib.	Ad lib.	Ad lib.
Spinach leaves	3 Gm. per rat per day in each diet					

The juice of California oranges and lemons was expressed fresh each day, strained through muslin, centrifugated at 1,000 revolutions per minute for thirty minutes and decanted. Twelve parts of orange juice by volume were mixed with one part of lemon juice, and the mixture fed in place of water in inverted bottles supplied with glass tubes adjusted to allow free drainage on suction but to minimize leakage.

Changes in the orange and lemon juice mixture on standing—alteration of flavor and increased turbidity—were an objectionable feature unavoidable under the conditions of feeding. Supplementary tests conducted with the juice mixtures under the feeding conditions indicated, however, that these changes probably did not influence the course of the experiment. Little or no change in p_H occurred.

8. Rosebury, T.; Karshan, M., and Foley, G.: J. Dent. Research **12**:464, 1932; **13**:379, 1933; J. Am. Dent. A. **21**:1599, 1934.

Cultures in neutral dextrose broth and on neutral dextrose agar and the tomato agar of Kulp and White[9] yielded no growth in some instances and occasional colonies of yeast and staphylococci in others, so that the change was apparently not fermentative. The animals that ingested the mixture, furthermore, although deprived of water, were equivalent in growth and survival to those on the control diet (76).

The two synthetic citrate mixtures used in diets 74 and 75 were prepared as controls for the acid-base, sugar and fluid content of the natural juices (74) and for the salt content in addition to the other factors (75). The acid-base properties of the natural juices were determined as follows:

(*a*) In determinations of the p_H the juice of four oranges and that of two lemons were tested separately and in 12 + 1 mixtures by means of the glass electrode with the following results: oranges, p_H 3.36 to 3.81, average 3.65; lemons, p_H 2.37 and 2.38; mixtures, p_H 3.13 to 3.45, average 3.32.

(*b*) In determining the organic acids a method suggested by Schlatter[10] was followed: Two 10 cc. samples of the juice of each of two oranges were neutralized with standard sodium hydroxide, phenolphthalein being used as indicator, and the neutral mixtures were transferred to platinum crucibles, evaporated to dryness and ashed. The ash was treated with a known excess (45 cc.) of standard sulphuric acid, made up to 50 cc., and a 25 cc. sample of this was neutralized with standard sodium hydroxide, phenolphthalein being used as indicator. Whole and centrifugated orange juices were found to agree closely. The method yielded the following values: titrated acid, 0.168 and 0.196 normal, with the average 0.182 normal; total organic acid, equivalent to 22.6 and 25.2 cc. of 0.1 normal sulphuric acid in 10 cc., or the equivalent estimated as 0.226 and 0.252 normal citric acid. Lemons were not tested, and the higher citric acid value, 0.25 normal, was selected for use.

(*c*) The composition of the edible portion of oranges was given by Bronson[11] as follows: water, 86.9 (per cent); protein, 0.8; fat, 0.2; carbohydrate and fiber, 11.6; ash, 0.5. Myers and Croll[12] found that California oranges contained 14.18 per cent sugar, made up of 8.1 per cent sucrose and 6.08 per cent reducing sugar. The latter values were used, the reducing sugar made up equally of dextrose and fructose.

(*d*) Bronson gave the percentage salt composition of the ash of California oranges as follows: potassium oxide, 48.94; sodium oxide, 2.50; calcium oxide, 22.71; magnesium oxide, 5.34; ferric oxide + aluminum oxide, 0.97; manganese oxide (Mn_3O_4), 0.37; phosphorus pentoxide, 12.37; sulphur trioxide, 5.25; silicon dioxide, 0.65; chlorine, 0.92. Since potassium is the predominating cation, synthetic mixture 1 (without added salts) was prepared as a simple citric acid and potassium citrate buffer with sugar added. Using the values derived, 50 cc. samples of 0.25 normal citric acid were titrated electrometrically with 5 times normal potassium hydroxide; 0.82 cc. of the latter was found required to produce p_H 3.3; this is equivalent to 4.53 Gm. of potassium hydroxide per liter of 0.25 normal citric acid. For mixture 2 we used 3 Gm. of potassium hydroxide per liter of

9. Kulp, W. L., and White, V.: Science **76**:17, 1932.

10. Schlatter, H., in Allen, A. H.: Commercial Organic Analysis, ed. 5, Philadelphia, P. Blakiston's Son & Co., 1923, vol. 1, p. 749.

11. Bronson, B. S.: Nutrition and Food Chemistry, New York, John Wiley & Sons, Inc., 1930.

12. Myers, V. C., and Croll, H. M.: J. Biol. Chem. **46**:537, 1921.

0.25 normal citric acid as calculated from the data on the ash, and the remaining salt values were calculated to correspond. Iron, aluminum and silicon were omitted. A separate salt mixture was prepared as follows from chemically pure ingredients, and 20 cc. added as a component of each liter of mixture 2.

Sodium chloride	7.6 Gm.
Sodium sulphate	19.3 Gm.
Magnesium sulphate	23.2 Gm.
Magnesium carbonate (basic: $3MgCO_3.Mg(OH)_2.3H_2O$)	43.7 Gm.
Tricalcium phosphate	134.5 Gm.
Calcium carbonate	72.5 Gm.
Distilled water to make	1,000 cc.

The two synthetic mixtures were prepared as follows:

	1 (Without Salts)	2 (With Salts)
Citric acid (M. W. 210.08)	21.7 Gm.	21.7 Gm.
Potassium hydroxide, electrolytic sticks	4.53 Gm.	3.0 Gm.
Salt mixture (as in the foregoing formula)	....	20.0 cc.
Sucrose	81.0 Gm.	81.0 Gm.
Dextrose	30.4 Gm.	30.4 Gm.
Fructose	30.4 Gm.	30.4 Gm.
Distilled water to make	1,000 cc.	1,000 cc.

Both mixtures were somewhat flat but not objectionable in taste and were well tolerated by the animals. They were prepared fresh at intervals of about a week, and the stock was kept in the refrigerator between feedings. They did not undergo detectable change on standing during these intervals. Several samples were tested for p_H by the glass electrode at intervals during the course of the experiment. The results ranged from p_H 3.25 to p_H 3.39, with the two mixtures in close agreement.

Dried lima beans were selected for use in diets 77 and 78 because they are somewhat similar both physically and chemically to rice; but instead of the slightly acid reaction of rice ash their ash has a strongly alkaline reaction, due chiefly to their higher content of potassium and sodium. The ash reactions of the dietary ingredients and of the diets as fed are given in the next paragraph. Diet 77 was not successful in that animals that ingested it did not survive more than twenty-two days of experimental feeding. The addition of ammonium chloride as 1, 1.5 and 2 per cent of the diet, respectively, with three successive groups of animals did not prolong survival. The results with this diet are consequently omitted from the tables but are mentioned in the body of the report.

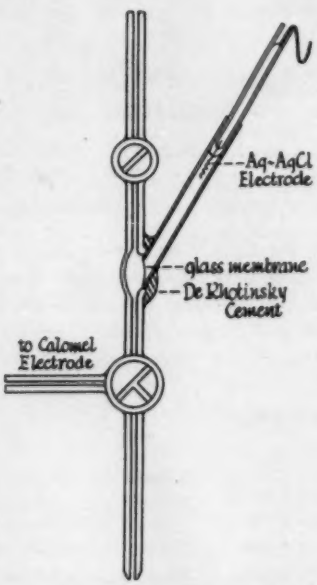
The food and fluid intakes were measured at intervals in all groups except 77. The food intake averaged 5.2 Gm. of dry diet per rat per day in all groups, and the fluid intake 6.4 cc. per rat per day, with no characteristic group differences. The intake of spinach per rat per day is estimated as 2 Gm. of the edible portion. To calculate the ash reactions of the diet as fed, the following values for dietary ingredients, given as cubic centimeters of normal acid or base per hundred grams, were used: rice, 9 acid (Sherman[13]); lima beans, 41.65 base (Sherman and Gettler[14]); orange juice and synthetic citrate 2, 8.6 base, and synthetic citrate 1, 8.1 base (both calculated from the data given), and spinach, 21.8 base (calculated from Sherman's data). These values yield the following for the ash reactions of the diets as fed in terms of cubic centimeters of normal acid or alkali per day: diets 73 and 75, 0.55 base; diet 74, 0.53 base; diet 76 (control), 0.01

13. Sherman, H. C.: Chemistry of Food and Nutrition, New York, The Macmillan Company, 1928.

14. Sherman, H. C., and Gettler, A. D.: J. Biol. Chem. **11**:323, 1912.

base, and diet 78, 0.65 base. The control thus appears to have been approximately neutral as fed, the acid effect of the rice having been counterbalanced by the spinach ingested, and all the experimental diets were definitely alkaline.

In an attempt to check these calculated values determinations were made during the course of the experiments on the p_H of the urine and the p_H and the carbon dioxide content of the blood plasma. Blood for these purposes was drawn by cardiac puncture under liquid petrolatum and transferred to oxalate tubes containing oil. These were centrifugated under solid paraffin. Urine was collected overnight by keeping the animal in an improvised metabolism cage consisting of a 10 pound (4.5 Kg.) tin with the bottom removed, set over a circle of 10 mesh wire gauze into a large glass funnel which had another circle of gauze placed at a lower level and sealed to the glass with paraffin. The stem of the funnel was connected by means of a rubber stopper with a separatory funnel below. The apparatus was



Glass electrode chamber for anaerobic determination of p_H of blood and urine.

filled with liquid petrolatum up to about the lower third of the tapered portion of the large funnel and about 1 cc. of toluene added. Animals were placed in groups of two in the tin in the evening, and the urine was removed and tested the following morning. The urine thus obtained was clear and normal in color and odor. All p_H determinations were made at 25 C. on the glass electrode by means of the vessel shown in figure 1. The plasma and urine samples under oil were allowed to stand in the constant temperature chamber (F. Rosebury [15]) for about fifteen minutes and were then aspirated into the vessel and the stopcocks closed. The vessel was washed between determinations by flushing it with 95 per cent alcohol and then with distilled water. By this procedure good checks were obtained with standard buffers. The values for p_H as given have been corrected to 37 C. by

15. Rosebury, F.: J. Indust. Engin. Chem. (Anal. Ed.) 4:398, 1932.

the method of Cullen.[16] Determinations of the carbon dioxide content were made on 0.2 cc. of plasma by the method of Van Slyke and Neill.[17]

The additional methods employed were the same as those previously used and described. The jaws and teeth of one lateral half of the mandible of each animal were sectioned and examined microscopically, the results for caries recorded by the use of the index value and the indexes compared by the statistical method outlined in the preceding report in this series.[18]

TABLE 2.—*The Incidence of Caries and the Average Values for Plasma p_H and for Carbon Dioxide and Urine p_H in Groups 73 to 78*

Group	Animals	Additions to Basal Diet	Experimental Period, Days	Caries: Animals, per Cent	Caries: Index	Plasma: p_H	Plasma: CO_2, Vol. per Cent	Urine, p_H
73	12	Orange-lemon juice ad lib.; no water	50-123	100	11.3 ± 1.1	7.30	61.2	6.80
74	11	Citrate mixture 1 ad lib.; no water (without salts)	50-130	100	10.2 ± 1.5	7.30	68.0	6.99
75	12	Citrate mixture 2 ad lib.; no water (with salts)	50-130	100	7.3 ± 1.4	7.33	66.9	7.09
76	10	None (control)	50-116	90	7.6 ± 1.8	7.34	65.8	6.80
78	11	Dried lima beans	50-130	81	6.9 ± 1.8	7.27	69.2	6.30
		McCollum stock diet (5 animals)				7.29	67.4	6.75

TABLE 3.—*Significance of the Effects on the Incidence of Caries of the Addition to the Basal Deficient Diet Containing 10 Mesh Rice, Dextrin and Spinach, of Orange and Lemon Juice, Citrate Mixtures, Dried Lima Beans and Sugars Other Than Dextrin*

Group	Animals	Caries Index m*	m_o	D	$\frac{D}{\sigma_D}$	Odds Against Random Occurrence of Difference
Pooled control	94	7.6 ± 0.6				
73	12	11.3 ± 1.1	8.0 ± 0.5	3.3 ± 1.2	2.8	195 to 1
74	11	10.2 ± 1.5	7.9 ± 0.5	2.3 ± 1.6	1.4	5 to 1
75	12	7.3 ± 1.4	7.6 ± 0.5	0.3 ± 1.5	0.2	<1 to 1
78	11	6.9 ± 1.8	7.5 ± 0.5	0.6 ± 1.9	0.3	<1 to 1
73, 74, 75	35	9.5 ± 0.8	8.1 ± 0.5	1.4 ± 0.9	1.6	8 to 1
30, 31	10	11.6 ± 1.3	8.0 ± 0.5	3.6 ± 1.4	2.6	106 to 1

* m, m_o, means; D, difference between two means; σ_D, standard deviation of D; values following $\pm$ signs are standard deviations. The deviation of these values and the method of analysis are described in the preceding paper in this series.[18]

RESULTS

Data on the incidence of caries, the p_H and the carbon dioxide determinations are given in table 2, and the significance of the results, in table 3. The values for plasma p_H and carbon dioxide and for urine p_H are within the normal range, as indicated by comparison with the values for animals on the modified McCollum stock diet. The calcification of

16. Cullen, G. E.: J. Biol. Chem. **52**:501, 1922.
17. Van Slyke, D. D., and Neill, J. M.: J. Biol. Chem. **61**:523, 1924.
18. Rosebury, T., and Karshan, M.: Arch. Path. **20**:697, 1935.

the teeth and bones of these animals, not recorded in the tables, was uniformly poor, and the separate groups were not mutually distinguishable on this basis. The levels and ratios of calcium and phosphorus in these diets are given in table 4.

The results as indicated in tables 2 and 3 were as follows: No significant reduction in the incidence of caries was obtained in any of the experimental groups as compared with the control or with the pooled control group used for more precise statistical analysis. Thus the reduction of caries expected in the group that received natural citrus juice was not obtained; instead the incidence of caries was increased in this group to an extent bordering on statistical significance. The three groups that received orange and lemon juice or a citrate mixture showed decreasing caries indexes from the group that received natural juice, with the highest index, to the group that received the citrate mixture plus salts, with the lowest index, but it is doubtful whether this trend is real or merely the result of random variation. These questions are discussed later in this paper.

TABLE 4.—*Levels and Ratios of Calcium and Phosphorus in Diets*

	Diet				
	73	74	75	76	78
Calcium	0.044	0.029	0.044	0.029	0.042
Phosphorus	0.255	0.247	0.255	0.247	0.267
Ratio	0.17	0.12	0.17	0.12	0.16

It has been noted that diet 77, in which ground rice was replaced entirely by dried lima beans ground to pass a 10 mesh sieve, did not allow survival for the period usually required with rice diets to produce the first fissure-caries lesions. In twenty-eight animals placed on the three modifications of this diet the period of survival ranged from three days to only twenty-two days. The jaws of all of these animals were nevertheless sectioned and examined microscopically, and it seems worthy of note that one of these animals, which had survived only seven days of experimental feeding, showed a characteristic fissure-caries lesion of stage 3 in the second molar. The third molar had not yet erupted. Over the lesion, impacted in the fissure, was a particle recognizable as lima bean by comparison with sections of beans made in different planes, and distinct from rice and spinach sectioned similarly.

COMMENT

It is clear from these results that the feeding of orange and lemon juice or synthetic mixtures similar in chemical composition but lacking protein, fat and vitamins exerts no protective action against dental caries

produced in rats with a coarse rice diet. With the natural juice and the synthetic mixture lacking added salts the incidence of caries was increased. If this increase is significant, it may be related to that produced in a previous experiment [8] when dextrose or saccharose was substituted for the dextrin in the basal diet (diets 30 and 31, table 3) and may depend on the added sugar in the diet. It is especially worthy of note in this connection that Shibata, as recently determined by Cox [19] from a direct translation of the original Japanese paper, reported that dextrose and saccharose were more effective in producing caries than dextrin. We had previously misinterpreted this statement in the English version of Shibata's report. These observations, augmented by the recent findings of Koehne, Bunting and Morrell [20] in children, suggest that the importance of different sugars in the caries-producing diet is worth further investigation. Additional studies on this phase of the subject are now in progress in this laboratory.

The result obtained with diet 78, which contained dried lima beans in addition to rice, both ground to pass a 10 mesh sieve, is interesting from two points of view: It appears, first, that in the absence of added sugar, which may have accelerated caries in diets 73 to 75, the incidence of caries was not altered with a diet having a definitely alkaline ash. The implication is clear that the reaction of the ash of the diet cannot be regarded as a factor in the production of experimental dental caries in rats. Furthermore, it appears likely, although not satisfactorily demonstrated by these results, that lima beans may have caries-producing properties similar to those of rice, as suggested by the fact that the incidence of caries in group 78 was not reduced despite reduction in the dietary proportion of rice, and by the finding of caries in a single instance on the rice-free diet 77.

SUMMARY AND CONCLUSIONS

Eighty-four rats 22 days of age were distributed among groups that received, respectively, the basal caries-producing diet containing 10 mesh rice, dextrin and spinach, and the following modifications of it: the basal diet with orange and lemon juice (12 + 1) fed ad libitum in place of water; the basal diet with a synthetic citrate mixture having the acid-base properties and sugar content of the natural citrus juice mixture; the basal diet with a synthetic citrate mixture having the acid-base properties and sugar and salt content of the natural juice; a diet in which all of the rice was replaced by 10 mesh dried lima beans, and a diet in which part of the rice was replaced by lima beans. The method

19. Cox, C. J.: Personal communication, 1934.

20. Koehne, M.; Bunting, R. W., and Morrell, E.: Am. J. Dis. Child. **48**:6, 1934.

of preparing the citrate mixtures has been described. The acid-base properties of the diets were calculated and the animals tested for the p_H and carbon dioxide content of the plasma and the p_H of the urine. The jaws and teeth of all the animals were studied microscopically for caries. The results appear to warrant the following conclusions:

The feeding of orange and lemon juice ad libitum in place of water with a caries-producing diet of 10 mesh rice did not reduce the incidence of caries but resulted in an increase of doubtful significance. This result was duplicated to less degree when the natural citrus juice was replaced by synthetic citrate mixtures having in one case the acid-base properties and sugar content and in the other the acid-base properties, sugar content and mineral content, of the natural juice. The increase of caries obtained, if significant, may depend on the fermentable sugar present in these mixtures.

A diet in which enough of the rice was replaced by dried lima beans to produce a mixture with a definitely alkaline ash did not yield a significantly lower incidence of caries than was obtained with the basal rice diet, which had an approximately neutral reaction as fed. A rice-free lima bean diet did not allow survival beyond twenty-two days of feeding but produced a typical lesion of fissure-caries in a rat that survived only seven days of experimental feeding.

RENAL LESIONS FOLLOWING INJECTION OF SODIUM DEHYDROCHOLATE IN ANIMALS WITH AND WITHOUT BILIARY STASIS

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In the course of our studies of biliary stasis and decompression in the cat [1] sodium dehydrocholate [2] was administered in order to investigate the effect of a bile salt of supposedly extremely low toxicity on certain hepatic lesions developing under those experimental conditions. To our surprise, a severe and rather characteristic lesion was uniformly found in the kidneys in animals with and without biliary stasis. Similar changes were found in dogs without stasis. These observations are of interest in connection with the controversial problem of epithelial regeneration in the kidney and in regard to the probable mechanism of diuresis which has been observed clinically following the administration of sodium dehydrocholate.

MATERIAL AND METHODS

Fifty-one cats (weighing from 1.3 to 4.3 Kg.) and four dogs (weighing from 6 to 15 Kg.) were employed in this study. They were maintained on a diet of fresh raw scrap meat and milk. Five series of experiments were performed, as follows:

EXPERIMENT 1.—Sodium dehydrocholate, in a 20 per cent solution, was injected into a vein in the leg in sixteen cats at twenty-four hour intervals over periods of from one to seventeen days, in individual doses of 0.2 cc. per kilogram of body weight. This dose would not be regarded as excessive for clinical use. The animals were killed by bleeding under light ether anesthesia twenty-four hours after the last previous injection of sodium dehydrocholate. Determinations of the

This investigation was aided by the Jefferson Medical College Hospital Tumor Clinic and the Martin Research Fund.

From the Department of Pathology, Jefferson Medical College and Hospital, and the Laboratory of Biochemistry, Jefferson Medical College Hospital.

1. (*a*) Cantarow, A., and Stewart, H. L.: Am. J. Path. **11**:561, 1935. (*b*) Stewart, H. L., and Cantarow, A.: Am. J. Digest. Dis. & Nutrition **2**:101, 1935. (*c*) Stewart, H. L.; Cantarow, A., and Morgan, D. R.: Arch. Path. **19**:807, 1935. (*d*) Stewart, H. L., and Lieber, M. M.: ibid. **19**:34, 1935. (*e*) Cantarow, A.; Stewart, H. L., and Lieber, M. M.: ibid. **20**:535, 1935.

2. Sodium dehydrocholate is available in the form of decholin sodium (obtainable from Riedel-de Haen, Inc., New York, which has been accepted by the Council on Pharmacy and Chemistry of the American Medical Association). The decholin employed in the present study was supplied by Mr. Paul de Haen.

nonprotein nitrogen were made on blood obtained at this time, and urine aspirated from the bladder was submitted to routine chemical and microscopic examination.

EXPERIMENT 2.—In three cats sodium dehydrocholate (0.2 cc. per kilogram of body weight, in a 20 per cent solution) was injected into a vein in the leg. The animals were killed by bleeding under light ether anesthesia two, three and four days, respectively, after injection. Specimens of blood and urine were examined as in experiment 1.

EXPERIMENT 3.—In three cats sodium dehydrocholate (0.2 cc. per kilogram of body weight, in a 20 per cent solution) was injected into the portal vein, which was exposed at laparotomy under ether anesthesia. The animals were killed by bleeding under light ether anesthesia one, two and three days, respectively, after injection. Specimens of blood and urine were obtained and examined as in experiment 1.

EXPERIMENT 4.—Sodium dehydrocholate (0.2 cc. per kilogram of body weight, in a 20 per cent solution) was injected daily into a vein in the leg in four dogs, which were killed by bleeding under light ether anesthesia twenty-four hours after one, two, three and four injections, respectively. Blood was obtained daily from the heart for determinations of the nonprotein nitrogen. No urine was present in the bladder in any case at autopsy.

EXPERIMENT 5.—In twenty-nine cats the common bile duct was ligated close to the duodenum at laparotomy under ether anesthesia. After twenty-four hours of biliary stasis sodium dehydrocholate (0.2 cc. per kilogram of body weight, in a 20 per cent solution) was injected into a vein in the leg. Individual animals received from one to fifteen injections during periods of stasis of from two to eighteen days; with the exception of a few instances of prolonged stasis in which a few injections were made at forty-eight hour intervals, they were given at intervals of twenty-four hours. The animals were killed by bleeding under light ether anesthesia twenty-four hours after the last previous injection. Specimens of blood were obtained and examined as in experiment 1. All cases were excluded from present consideration in which there was any evidence of infection or of patency or reconstruction of the common duct or entrance of bile into the intestine through anomalous or accessory ducts.

Pieces of tissue were fixed in a dilute solution of formaldehyde U. S. P. (1 : 10) or solution of formaldehyde with Zenker's solution. Some were subsequently frozen, cut and stained with nile blue sulphate and scarlet red, the remainder being blocked in paraffin, cut and stained with hematoxylin and eosin and Mallory's connective tissue stain.

EXPERIMENT 1

Observations were made on sixteen cats killed twenty-four hours after from one to fifteen injections into a vein in the leg.

Gross Observations.—The kidneys were swollen to a moderate degree after from one to eight injections but were either normal in size or smaller than normal in animals receiving a greater number of injections. The surface, which was rather uniformly yellow in the early stages, tended to be more definitely brown in the later stages. The cut surface was consistently edematous, and the tissue was soft in consistency. The cortex was relatively narrow, even in kidneys that were increased in size, this change becoming progressively more marked with increasing numbers of injections; in the later stages, the thickness of the cortex was diminished by from 30 to 40 per cent. In the shorter experiments (from one to eight injections) the outer zone of the medulla frequently showed fine bright red punc-

tate and linear markings; later, fine gray striations were occasionally noted in this situation.

Microscopic Observations.—By far the most outstanding histologic changes occurred in the tubules, which showed variable degrees of dilatation and degeneration and evidences of regeneration of the lining epithelium. Relatively minor changes were noted in the interstitial tissue of the outer medullary and inner cortical zones, which showed evidence of a mild inflammatory reaction, with vascular congestion, edema, slight infiltration by cells and, in the later stages, increase in connective tissue. Glomerular lesions were inconstant and relatively inconspicuous and in no instance resembled those characteristic of glomerulonephritis.

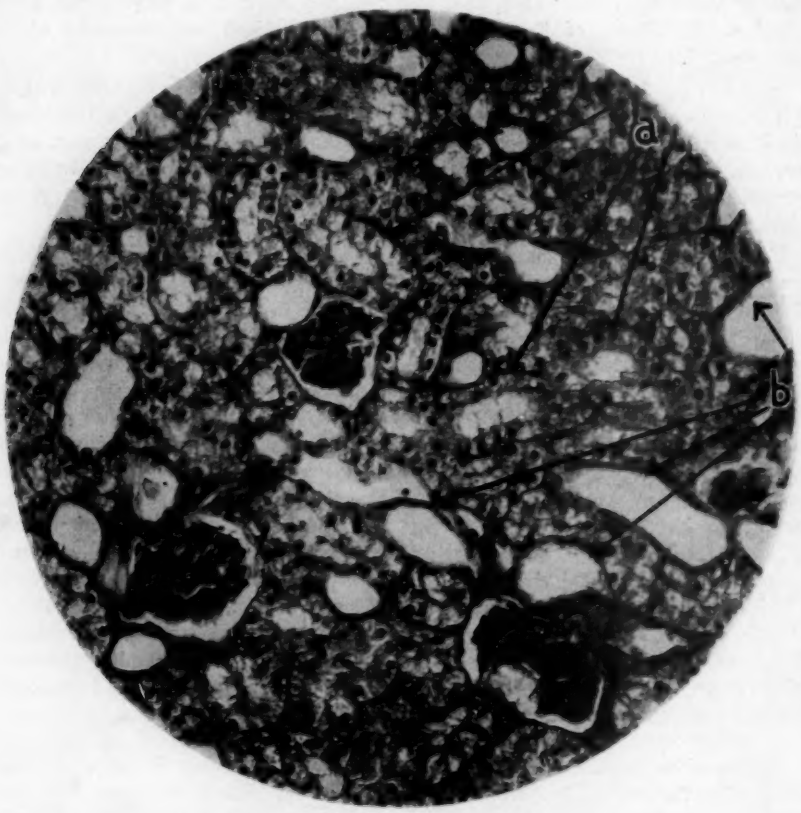

Fig. 1.—Section of kidney showing (*a*) tubules with increased outside diameter and (*b*) tubules with increase in the diameter of the lumen associated with flattening of the lining cells. Many cells show hydropic degeneration and necrosis. Magnification, about 200 ×.

Dilatation of Tubules: Some increase in the outside diameter of the tubules was noted throughout the entire course of the experiment. This was frequently diffuse but in some instances was particularly marked in localized portions of the tubule. This dilatation was prominent after a single injection and persisted as a prominent feature in animals receiving seven or eight injections, decreasing subse-

quently but still being present to a variable degree. The diameter of the lumen was also increased, this increase being proportional both to the increase in outside diameter and to the diminution in the height of the lining cells, described in the next section (figs. 1 and 2).

Regressive Changes in Tubular Epithelium: Marked regressive changes were present in the tubular epithelium in every case. The intensity of these changes did not increase in proportion to the number of injections, but rather appeared to be related to the nature of the epithelial cell predominating in each case; i. e., there was a variable degree of susceptibility of the various forms of regenerated

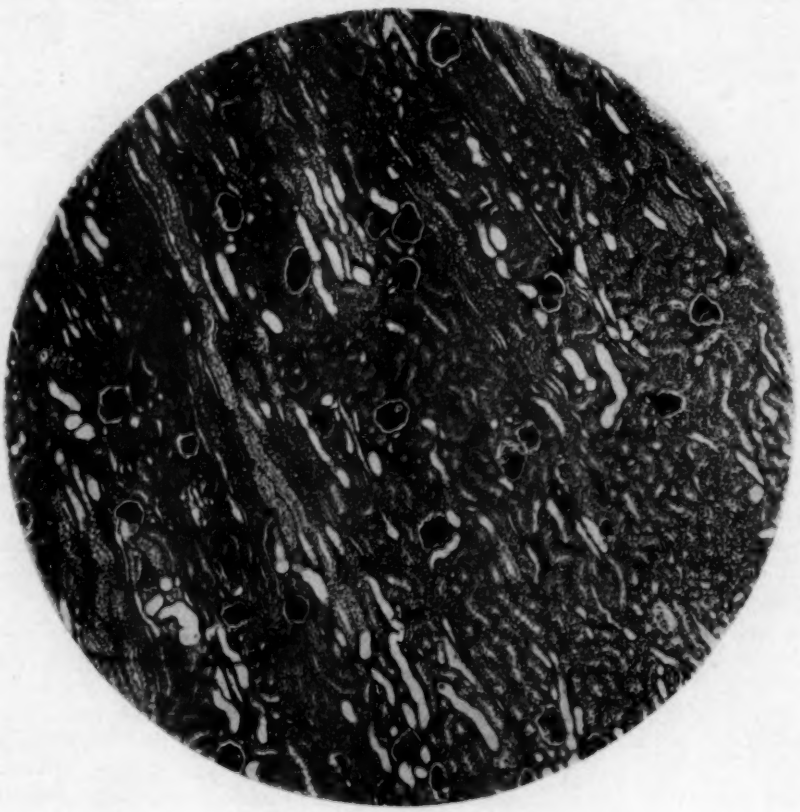

Fig. 2.—Section of kidney showing extensive dilatation of tubules, flattening of epithelial cells and pale, reticular character of certain cells lining straight tubules. Magnification, about 50 ×.

cells to subsequent injury. Some degree of regressive change, however, was observed in different instances both in atypical regenerated and in normal-appearing cells. In many cases, particularly in the early stages, the process was generalized, but in some instances following several injections it appeared to be more intense in the straight tubules of the inner cortical and outer medullary zones.

After a single injection there were extensive degeneration and necrosis of the cells that could be recognized as apparently the original tubular epithelial cells.

In the early stage of the degenerative process the cell was swollen and was either homogeneous and acidophilic or hydropic, with pale, granular and reticulated cytoplasm and curvilinear striations, the long axis of the cell being tilted in relation to the basement membrane (figs. 1 and 2). As the regressive process progressed the nuclei showed the characteristic evidences of necrosis, the cellular outlines became obliterated and cytoplasmic disintegration, beginning at the free border, progressed inward, leaving a ragged luminal outline and, in occasional tubules, a completely denuded basement membrane. Degenerative changes were most extensive after one or two injections, involving particularly the original lining cells of the tubules. With increasing numbers of injections (from five to eight) the predominating type of epithelium was of the atypical, flattened form described later (under regeneration) which, although apparently resistant to subsequent injury, nevertheless was involved in the regressive process to a variable extent in certain cases. In the late stages (twelve or more injections) a large proportion of the tubules were lined by tall columnar cells which resembled the original cells, and in these the intensity of degeneration and necrosis sometimes approached that observed after a few injections.

The lumens of the tubules contained shreds of lining membrane, hyaline droplets, albuminous material and casts, and in some instances they were filled with cells, desquamated singly or *en masse*. Calcific deposits were frequently observed within the lumens of the tubules and at times in necrotic lining cells in both the cortex and the medulla.

Regeneration of Tubular Epithelium: Evidences of regeneration were obtained in every instance in all stages of the experimental period. This was characterized particularly by the development of an atypical form of regenerated cell, which was present in all cases, and in some instances in great numbers, after a single injection. These atypical cells, when first formed, were exceedingly flat when viewed in cross-section; their nuclei were two or three times the normal size; they were usually oval but sometimes round, the long diameter being sometimes vertical, sometimes parallel and sometimes situated obliquely to the basement membrane. The relatively large size of the nuclei in proportion to the cytoplasm caused them to protrude into the lumen of the tubules, producing a beadlike appearance. When cut tangentially, these cells appeared large, oval or round, sometimes irregular, with a slightly basophilic cytoplasm and a pale nucleus containing numerous fine particles of chromatin, one or more dense masses of chromatin and sometimes vacuoles (fig. 3). These flat cells were observed in all portions of the renal tubule in different animals. In the early period of the experiment (from one to three injections) they tended to occur in groups of tubules in triangular areas in the outer layer of the cortex, the base lying toward the surface of the kidney. In the later period they were more diffusely distributed, but involved particularly the tubules in the inner cortical and outer medullary zones. This markedly flattened cell was most numerous in animals receiving from four to seven injections, the great majority of the tubules in some cases being lined by this type of epithelium. In the later stages these cells usually diminished in number.

Other atypical forms of epithelial cells were present throughout the course of the experiment. These appeared to represent transition stages between the very flat cells already described and the mature tubular epithelium. They varied in height from low cuboidal to tall columnar types, the cytoplasm becoming less basophilic as the cell increased in height. The nuclei became smaller and rounder as the height of the cell increased, the arrangement of chromatin simultaneously changing from that noted in the case of the flat cells to one approaching normal,

with a distinct tendency toward hyperchromasia. In many instances single tubules were lined by flat, cuboidal and columnar cells, the nuclei of which were situated at different levels in relation to the basement membrane, imparting an extremely irregular appearance to the epithelial lining. Syncytial masses of cells possessing all the characteristics of viable, newly regenerated cells, as already described, were observed, particularly in the tubules of the inner layer of the cortex and the outer layer of the medulla; these at times practically occluded the lumen of the tubule. These cells could be readily differentiated from degenerated and necrotic masses of cells desquamated into the lumen.

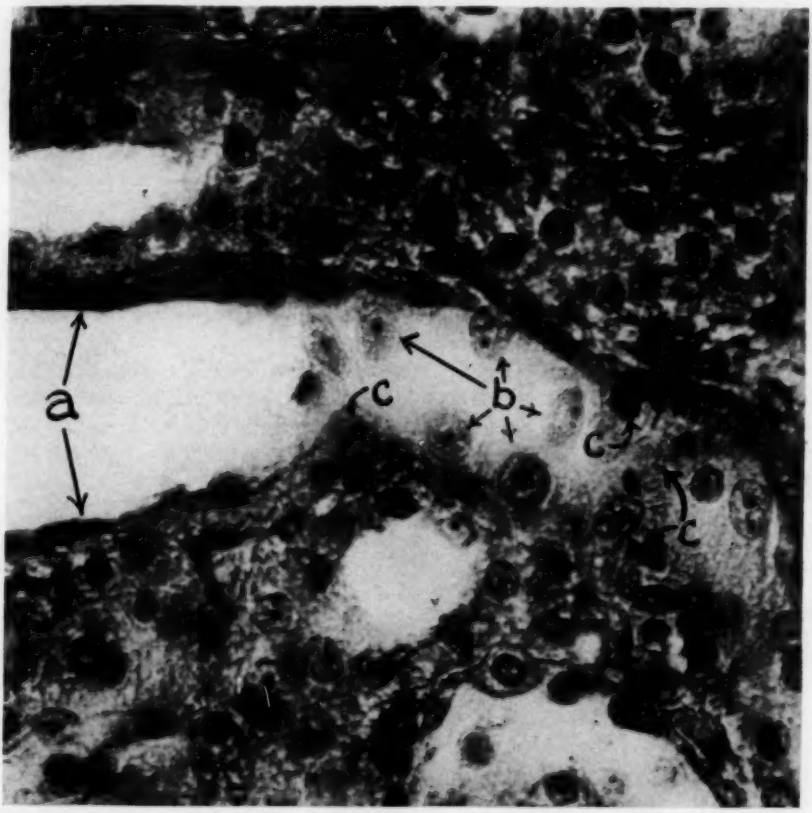

Fig. 3.—Section of kidney, with tubule crossing field from left to right, showing flattened type of atypical regenerated cell (*a*) in cross-section and (*b*) cut tangentially and (*c*) four mitotic figures in the same plane. Magnification, about 750 ×.

Mitotic figures were observed in association with all varieties of epithelial cells, both atypical and normal, in all portions of the tubule, being most consistently present and most numerous in the tubules of the inner cortical and outer medullary zones (fig. 3). They were noted at every stage of the experiment, although not in every animal, being most numerous after from two to seven injections and decreasing subsequently except in one case in which large numbers were seen

after twelve injections. In some places these dividing cells appeared to be growing beneath the degenerated cells of the original lining membrane, but at times they projected into the lumen of the tubule. In some cases cells undergoing mitosis were scattered singly throughout the renal tissue, while in others several such cells were present in a single tubule.

Interstitial Tissue: Changes in the interstitial tissue were limited particularly to the outer layer of the medulla and the inner layer of the cortex, being less constant and less marked in the latter situation. These changes were apparently inflammatory, consisting of capillary congestion and thrombosis, edema, cellular infiltration and fine fibrosis of the interstitial tissue. No fibrin was observed in any instance. After a single injection the intertubular capillaries in these situations were dilated, hyperemic and occasionally thrombosed and contained an increased number of polymorphonuclear leukocytes. Few or no inflammatory cells were noted in the interstitial tissue during this period. After two or more injections edema, cellular infiltration and a fine fibrosis developed, these changes being distributed generally throughout the region of the corticomedullary junction, with focal areas of increased involvement, particularly in the outer layer of the medulla. Edema was most marked after from six to eight injections and in some instances was so extensive as to cause compression of the surrounding tubules. Fibrosis was never extensive, but cellular infiltration was marked after from fourteen to sixteen injections, the predominating cells being mononuclear leukocytes and lymphocytes. In a few cases polymorphonuclear and mononuclear leukocytes were observed in the lumens of the tubules in this region.

Glomeruli: Morphologic evidence of glomerular damage was absent in most cases and when present was slight and inconstant. There were variable changes in size, cellularity and congestion of glomerular tufts in different cases as well as in different portions of the kidney in individual animals. These changes bore no consistent relation to the number of injections or to the degree of involvement of the remainder of the kidney. The capsular spaces were at times dilated and at times small and frequently contained acidophilic granular material, hyaline droplets and desquamated cells. The parietal cells were often desquamated, and the capsule was frequently lined by pale, flat or cuboidal basophilic cells which resembled the newly regenerated cells of the renal tubules. At times these cells were arranged in syncytial masses and were occasionally observed in mitosis. In a few animals in the late stages an occasional glomerulus in the deep layer of the cortex was involved in the inflammatory and fibrotic process occurring in this area.

Stainable Lipid: The distribution of stainable lipid in fourteen nonpregnant adult animals was as follows: (1) convoluted tubules only, two cases; (2) convoluted and Henle tubules, seven cases; (3) convoluted, Henle and collecting tubules, five cases. Fatty casts were present in large numbers in two cases, and in one instance remnants of the old necrotic, desquamated lining membrane within the lumens contained numerous droplets of lipid, while the atypical regenerated lining cells of the same tubules contained no stainable lipid. Stainable lipid was found in the extremely flat variety of regenerated epithelium in only one case, but it was occasionally present in transitional forms. In several instances a large proportion of the convoluted tubules contained no stainable lipid.

Blood and Urine.—We have obtained values for the nonprotein nitrogen of the blood as high as 55 mg. per hundred cubic centimeters in apparently normal cats. In five cats, twenty-four hours after a single injection of sodium dehydrocholate the values for the nonprotein nitrogen of the blood were as follows: 30, 46, 114, 127

and 148 mg. per hundred cubic centimeters, the corresponding values for creatinine being 1.4, 1.7, 5.4, 3.2 and 2.6 mg., respectively. In ten animals receiving from two to fifteen injections the concentration of the nonprotein nitrogen ranged from 30 to 67 mg., being below 55 in six and above 55 in four instances. The level of the nonprotein nitrogen of the blood bore no demonstrable relation to the number of injections after the first injection.

The urinary findings were extremely variable. Several specimens were apparently normal; others contained from a trace to a heavy cloud of albumin, from a few to many hyaline and granular casts per low power field and from 15 to 60 pus cells per low power field.

EXPERIMENT 2

Observations were made on three cats killed two, three and four days following a single injection into a vein in the leg.

Grossly, the kidneys resembled those described previously. In the cat killed two days after the injection there were moderate edema, degeneration and necrosis of the tubular epithelium, with marked desquamation of the lining cells and occasional deposits of calcium. Regeneration of atypical flattened cells was relatively slight, and mitotic figures were occasionally seen. A few casts were seen in the tubules, and there was evidence of a mild inflammatory reaction in the region of the corticomedullary junction. Dilatation of the tubules and regressive changes in the tubular epithelium were less marked than in animals studied twenty-four hours after a single injection, as described previously.

In the cat killed three days after a single injection there was marked, diffuse dilatation of the tubules, about 35 per cent of which were lined by the flattened, atypical variety of regenerated epithelium, chiefly cuboidal. There were a moderate degree of degeneration, some calcification and marked edema of the tubular epithelial cells. Many mitotic figures were observed. There was a mild inflammatory reaction in the outer medullary interstitial tissue.

In the cat killed four days after a single injection all regressive changes were distinctly less severe than in the cat killed three days after the injection. There was but slight dilatation of the tubules of the cortex and outer layer of the medulla, many of which were lined by cells which, although not markedly flattened, could be readily recognized as newly regenerated cells, apparently approaching normal in size, shape, staining reaction and nuclear characteristics. In places these cells were arranged in syncytial masses which occupied the entire lumen of the tubule. No mitotic figures were observed, and there was little if any evidence of inflammatory reaction in the interstitial tissue.

Stainable lipids were present in the epithelium of both the Henle and the convoluted tubules in each case. In the cat studied three days after the injection fine granules of lipid were observed in the very flat and cuboidal varieties of atypical regenerated epithelium.

The concentrations of the nonprotein nitrogen of the blood two, three and four days after a single injection of sodium dehydrocholate were 46, 59 and 52 mg. per hundred cubic centimeters, respectively. The urine of the cat killed after two days was essentially normal; that of the cats killed on the third and fourth days contained a light cloud of albumin and an occasional hyaline and granular cast and from 15 to 20 pus cells per low power field.

EXPERIMENT 3

Observations were made on three cats killed one, two and three days after a single injection into the portal vein.

In the cat killed one day after injection there was moderate dilatation of the tubules, with marked degeneration, necrosis and desquamation of the lining cells. There was a moderate degree of regeneration of the atypical, flattened variety of epithelium, and no mitotic figures were seen. The tubules contained numerous casts, and the inflammatory reaction in the interstitial tissue was of mild degree. These changes closely resembled those observed in animals studied twenty-four hours after a single injection into a vein in the leg.

Two days after the injection practically all the tubules showed an extreme grade of dilatation, about one third of the lining cells being of the atypical, flattened variety. Large numbers of mitotic figures were present. Regressive changes were less severe than in the cat killed one day after the injection. A few areas of calcium deposition were observed, and there was a mild inflammatory reaction in the interstitial tissue of the outer layer of the medulla.

In the cat killed three days after injection, dilatation and degeneration were distinctly less marked than in the cat killed two days after the injection. The number of atypical, regenerated epithelial cells was approximately the same, but the majority of these were cuboidal rather than markedly flattened and were definitely more normal in appearance. No mitotic figures were seen.

Stainable lipids were present in the epithelium of both the convoluted and the Henle tubules in each case and also in the collecting tubules in the animals studied three days after injection. Although the transitional type of epithelium contained some lipid material, none was observed in the extremely flat cells.

The concentrations of the nonprotein nitrogen of the blood one, two and three days after a single injection into the portal vein were 34, 55 and 40 mg. per hundred cubic centimeters, respectively. The urine of the cats killed one and two days after the injection was essentially normal; that of the cat killed on the third day after the injection contained a trace of albumin, an occasional hyaline and granular cast and from 50 to 60 pus cells per low power field.

EXPERIMENT 4

Observations were made on four dogs killed twenty-four hours after one, two, three and four injections, respectively, into a vein in the leg.

With certain minor exceptions, the changes in the kidneys closely resembled those observed in cats studied under similar conditions. Grossly, there was marked edema. Dilatation of the tubules, although distributed equally widely, was not as marked as in cats receiving the same number of injections. Edema, degeneration and necrosis of the tubular epithelial cells were uniformly present and appeared to be more severe than in the cat. Atypical forms of regenerated epithelium were noted in all cases, but mitotic figures were extremely scarce. A mild inflammatory reaction was present in the interstitial tissue of the medulla and walls of the calices and pelvis, the predominating types of infiltrating cells being plasma cells and mononuclear leukocytes. As in the cat, glomerular changes were inconspicuous.

Small quantities of stainable lipid were present in each case in the cells of the Henle tubules and in three cases (one, two and four injections) in the epithelium of a few convoluted tubules. Fatty casts were present in the medullary tubules in one case (two injections). Stainable lipids were not observed in the atypical forms of regenerated epithelium.

The values for the nonprotein nitrogen of the blood were as follows:

Dog 1.—Control, 40 mg.; four hours after injection, 49 mg.; twenty-four hours after injection, 34 mg.

Dog 2.—Control, 28 mg.; four hours after injection, 44 mg.; twenty-four hours after injection, 52 mg.; two days after injection, 38 mg. (twenty-four hours after the second injection).

Dog 3.—Control, 42 mg.; four hours after injection, 56 mg.; twenty-four hours after injection, 28 mg.; two days after injection, 30 mg. (twenty-four hours after the second injection); three days after injection, 32 mg. (twenty-four hours after the third injection).

Dog 4.—Control, 37 mg.; four hours after injection, 46 mg.; twenty-four hours after injection, 33 mg.; two days after injection, 29 mg. (twenty-four hours after the second injection); three days after injection, 36 mg. (twenty-four hours after the third injection); four days after injection, 28 mg. (twenty-four hours after the fourth injection).

EXPERIMENT 5

Observations were made on twenty-nine cats with total biliary stasis (for from two to eighteen days) killed twenty-four hours after from one to fifteen daily injections into a vein in the leg of 0.2 cc. of sodium dehydrocholate (a 20 per cent solution) per kilogram of body weight. The periods of stasis and injection were concurrent, the injections being started twenty-four hours after ligation of the common bile duct.

Gross Observations.—After a single injection (stasis of two days) the kidneys were swollen, the cortex was wide and pigmentation was relatively slight. Subsequently the kidneys were frequently of normal size or smaller than normal; the cortex was usually narrow, and pigmentation was rather consistently intense, varying from deep brown to the characteristic grass green seen in total biliary stasis. The surface of the kidney presented a peculiarly mottled appearance, with irregular areas of more intense pigmentation superimposed on a diffusely stained background, the mottling being most conspicuous toward the pelvis; at times these more deeply colored areas tended to become confluent. Edema of the cut surface, although noted occasionally, was in no instance a prominent feature.

Occasionally the green-brown color of the cut surface of the cortex was relieved by pale striations running perpendicularly to the surface of the kidney. In many cases the medulla immediately beneath the cortex presented a narrow red or brownish-red zone of vascular hyperemia, which in some animals extended slightly into the cortex. The tips of the pyramids were usually light or dark brown, the area of medullary tissue intervening between the zone of hyperemia and the tips of the pyramids usually being pale.

Microscopic Observations.—Pigmentation: The intensity of pigmentation varied in individual cases, but in general those animals in which biliary stasis was prolonged presented a marked degree of pigmentation more consistently than those in which stasis was of brief duration. In some cases the bile pigment occupied the tubular epithelial cells diffusely, no definite granules being demonstrable, while in others it was present in the form of light yellow or brown granules. The pigmentation was generalized in distribution, all portions of the tubule being involved. Bile-stained casts were noted in various situations, and the desquamated epithelium and precipitated protein material within the lumens were frequently bile-stained.

Dilatation of Tubules: Increase in the outside diameter of the tubules was particularly marked after from six to eight injections but was not a prominent feature during the earlier and later stages of the experiment. Increase in the diameter of the lumen varied considerably, being dependent on the height of the lining epithelium as well as on the outside diameter of the tubule.

Regressive Changes in Tubular Epithelium: Marked regressive changes were present in every case. As in the animals without biliary stasis, the intensity and extent of these changes did not increase in proportion to the duration of the experiment but appeared to be related to the relative proportions of typical and atypical forms of epithelium present in each instance. The morphologic characteristics of the degenerated and necrotic cells were similar to those described in connection with these changes in the kidneys of animals without biliary stasis. However, certain minor differences were noted. The homogeneous type of cell was generally more intensely acidophilic; the hydropic, reticulated cells stood out more prominently, and superimposed on these features there was a variable but rather consistently marked degree of bile pigmentation. Bile-stained casts, desquamated, degenerated epithelium, hyaline droplets and albuminous material were frequently seen within the lumens of the tubules. Calcified deposits were rarely observed.

Regeneration of Tubular Epithelium: Evidences of regeneration of tubular epithelium were present in every instance, the essential features being identical with those described previously in connection with the groups of animals without biliary stasis. All varieties of the atypical, newly regenerated epithelial cells were observed. The largest proportion of extremely flat cells was noted in an animal receiving seven injections, but relatively large numbers of atypical cells were observed in all cases throughout the course of the experiment. Mitotic figures were exceedingly numerous in all stages after the second injection, in one case as many as thirteen being noted in a single high power field. The regenerating cells were occasionally piled up in syncytial masses.

Interstitial Tissue and Glomeruli: The interstitial tissue and glomeruli presented much the same appearance as in the groups of animals described previously. Interstitial fibrosis was never marked, and the glomerular tufts showed no evidence of significant structural damage.

Stainable Lipid: The distribution of stainable lipid in twenty-two adult, nonpregnant cats receiving from one to fifteen injections (stasis of from two to eighteen days) was as follows: (1) convoluted tubules only, two cases (a single injection and stasis of two days); (2) convoluted and Henle tubules, ten cases; (3) convoluted, Henle and collecting tubules, seven cases; (4) Henle and collecting tubules, one case; (5) convoluted and collecting tubules, two cases. Stainable lipid was never observed in the extremely flat variety of atypical regenerated epithelium.

Blood Nonprotein Nitrogen.—Values for the nonprotein nitrogen of the blood ranging from 29 to 42 mg. per hundred cubic centimeters were obtained in seventeen cats receiving from two to fifteen injections (stasis of from three to eighteen days).

It seems evident that sodium dehydrocholate, injected intraveously, is actively nephrotoxic for the cat and dog. In the cat the renal changes following a single injection into the portal vein were identical, qualitatively, and quantitatively, with those which followed a single injection into a vein in the leg. The process was essentially degenerative; it involved the epithelial cells of the tubules throughout their entire extent and was particularly marked in the region of the corticomedullary junction. There were inconstant and relatively inconscpicuous degenerative changes in the glomeruli in some instances and evidences of a mild

inflammatory reaction and fibrosis in the interstitial tissue of the outer medullary zone.

Of particular interest were changes in the tubular epithelium indicative of active regeneration. The morphologic characteristics of the regenerated cells were similar to those described by Suzuki,[3] Oliver,[4] MacNider,[5] Hunter [6] and MacKay and Oliver [7] and others in connection with the nephrotoxic effects of a variety of substances, such as uranium nitrate, mercury bichloride, potassium bichromate and sodium phosphate. As early as twenty-four hours after a single injection of sodium dehydrocholate an extensive degenerative lesion was accompanied by the development of a flattened type of newly regenerated epithelium. At this time these atypical cells, although not extremely numerous, were predominantly of the very flat variety. Within a four day period following one injection the intensity of the degenerative process gradually subsided and the number of atypical newly regenerated cells increased, reaching a maximum on the third day, at which time they constituted approximately 35 per cent of the lining cells of the renal tubules. Mitotic figures were also most numerous at this period (three days), being present in association with both mature and atypical forms of epithelial cells. The relative proportion of the extremely flat type of cell steadily diminished, being replaced by cuboidal cells and, on the fourth day, distinctly columnar cells which, although obviously newly regenerated, were approaching normal in size, shape, staining reaction and nuclear characteristics. The impression was obtained that the flat cells, constituting the original regenerative response, gradually and progressively developed into the cuboidal and columnar forms and eventually acquired all the characteristics of mature renal epithelial cells. This is in accord with the observation of Addis and Oliver [8] of a similar transition from atypical to mature forms of epithelium in animals receiving a single injection of nephrotoxic mineral salts.

The studies of MacNider,[5] Hunter,[6] Hunter and Roberts [9] and others have led to the now generally accepted concept that the atypical form of regenerated epithelium which develops in response to the nephrotoxic action of certain substances (mercury bichloride, uranium salts, potassium bichromate) is resistant to the toxic effects of subsequent admin-

3. Suzuki, T.: Zur Morphologie der Nierensekretion unter physiologischen und pathologischen Bedingungen, Jena, Gustav Fischer, 1912.

4. Oliver, J.: J. Exper. Med. **21**:425, 1915.

5. MacNider, W. deB.: J. Exper. Med. **49**:411, 1929.

6. Hunter, W. C.: Ann. Int. Med. **2**:796, 1929.

7. MacKay, E. M., and Oliver, J.: J. Exper. Med. **61**:319, 1935.

8. Addis, T., and Oliver, J.: The Renal Lesion in Bright's Disease, New York, Paul B. Hoeber, Inc., 1931, pp. 125 and 126.

9. Hunter, W. C., and Roberts, J. M.: Am. J. Path. **9**:133, 1933.

istration of these agents. This belief is substantiated by the observations made in the present study. In animals receiving repeated injections of sodium dehydrocholate at intervals of twenty-four hours, regressive changes were not observed in the extremely flat type of immature cell, even though the mature cells throughout the renal parenchyma showed evidences of an advanced stage of degeneration. Immature cells which were apparently transitional between the very flat variety and the mature, columnar form showed degenerative changes to a variable degree but were apparently less susceptible than the original renal epithelium to the nephrotoxic effect of sodium dehydrocholate. After the original exposure, therefore, the morphologic character of the renal response to subsequent injections was influenced to a large extent by the relative proportions then present of three classes of epithelial cells, i. e., (1) those with little if any resistance (original, mature form), (2) those with variable but increased resistance (transition forms of regenerated cells) and (3) those with a high degree of resistance (extremely flat regenerated forms). In view of the fact that after from six to eight injections the great majority of the tubules were lined by the very flat type of epithelium, it is probable that but few of the taller, more mature cells that predominated in the later stages of the experiment were cells originally present in the kidney. It is interesting to note that regressive changes, although present in these taller forms of epithelium after from twelve to fourteen injections, were not as severe or as extensive as those noted after a single injection. This observation is in accord with the hypothesis of diminished susceptibility of the newly regenerated atypical cells to the effects of repeated exposure to a nephrotoxic agent.

The renal changes observed in animals with total biliary stasis were essentially similar to those occurring in animals without obstruction of the common bile duct, with certain exceptions. The severity and extent of degeneration were not significantly influenced by the state of biliary stasis. Regeneration, on the other hand, was apparently more active, mitotic figures particularly being much more numerous. The explanation of this point of difference is not readily apparent, for in a previous study [1c] no evidence of active regeneration and no mitotic figures were observed in the kidneys of cats with total uncomplicated biliary stasis. Bile pigmentation of the kidneys was definitely more intense in animals with biliary stasis receiving dehydrocholate than in those studied previously.[1c]

The marked dilatation of the tubules, which was a rather constant finding following the administration of sodium dehydrocholate, resembled in certain respects that noted by us [1c] following decompression of the obstructed biliary system of the cat. However, diminution in the height of the lining epithelium under the latter circumstances was apparently due to actual mechanical stretching rather than to the develop-

ment of atypical forms of regenerated cells. One point of interest and possibly of significance is the fact that calcific deposits, which were not a conspicuous feature in the kidneys of the animals with biliary stasis which received injections, were extremely numerous in one animal with spontaneous decompression. It is possible that calcific deposits in animals with total stasis may have been obscured to some degree by deeply pigmented bile casts.

The effect of sodium dehydrocholate differs from that generally reported in the case of uranium salts in that it is apparently exerted on the epithelium of the renal tubule throughout its entire extent. According to Hunter and Roberts,[9] regeneration does not usually occur before from four to six days after the administration of uranium and mercury, and Addis and Oliver [8] stated that the flat, newly regenerated cells begin to assume mature characteristics about the end of the second week. With the administration of sodium dehydrocholate, regeneration apparently occurs much more rapidly, the extremely flat type of cell being present in abundance within twenty-four hours and a gradual transition toward the mature form beginning almost immediately. On the fourth day after a single injection transition forms predominate, comparatively few cells being of the extremely flat variety.

There has been considerable controversy regarding the nature of the mechanism which prevents the markedly atypical forms of regenerated cells from attaining maturity in animals receiving nephrotoxic mineral salts. Addis and Oliver [8] stated:

> Although it has been suggested that the cause of this continued abnormality on the part of the developing cells might be sought in some toxic effect of the uranium on the germ plasm of the new cells, . . . to us a more rational and simpler explanation seems to be an interference with their growth or nutrition by the proliferating connective tissue which is at the same time developing side by side with the epithelial structures.

Hunter and Roberts [9] subscribed to this view. In this connection it is interesting to note that in the present experiments proliferation of connective tissue was practically absent in the cortex, and in this situation there appeared to be little if any inhibition to the progressive development of atypical regenerated cells into mature forms. This observation would appear to support the hypothesis advanced by Oliver.[4]

Modell and Travell [10] found that uranium intoxication in cats was accompanied by the development of an abnormal distribution of stainable lipids in the kidney. These substances, which are normally confined to the epithelium of the convoluted tubules, increased in amount in this situation and, in addition, extended into the cells of the Henle tubules.

10. Modell, W., and Travell, J.: Anat. Rec. **59**:253, 1934.

A similar abnormality of distribution was reported by us [1c] in cats during biliary stasis and decompression. It was suggested [11] that the appearance of lipids in the epithelium of the Henle and collecting tubules probably was not a part of a regressive process but rather was related to metabolic changes or to an alteration in the functional activity of the tubular epithelium. The observations in the present experiment resemble those previously described in animals with nephritis due to uranium and with biliary stasis and decompression. Because of the presence of degenerative changes throughout all portions of the renal tubule, no further light is thrown on the pathogenesis of the altered distribution of lipid. It is of interest to note that stainable lipid was rarely observed in the extremely flat variety of the atypical regenerated cell, increasing in amount as the cell became more mature. This may be related in some way to the development of functional activity by these cells.

In many instances the presence of functional or morphologic renal injury was evidenced by the appearance of albumin and casts in the urine. The fact that the most marked grades of nitrogen retention were generally observed within twenty-four hours after the first injection of sodium dehydrocholate suggests that the most severe functional injury is associated with the extensive initial degenerative changes in the original renal epithelial cells. The subsequent subsidence of the level of the nonprotein nitrogen of the blood in most cases, despite repeated injections of dehydrocholate, suggests that the atypical regenerated cells possess some degree of functional activity. Unfortunately, no functional studies were made after a single injection in animals with biliary stasis; however, the absence of nitrogen retention in seventeen such animals receiving from two to fifteen injections was in striking contrast to its presence in four of ten cats without biliary stasis which received multiple injections. It is of interest in this connection that the activity of regeneration was generally greater in the former than in the latter.

In view of the numerous observations of the pronounced choleretic effect of sodium dehydrocholate and in view of the probability that it is eliminated, to some extent at least, in the bile, it seems strange that relatively little difference in nephrotoxic effect was noted in the animals with and without biliary stasis. The question may be raised whether this substance may not undergo repeated excretion and reabsorption by the kidney, its elimination by the liver occurring gradually. This hypothesis is strengthened by the observation that the changes in the kidney which followed the injection of dehydrocholate into the portal vein were practically identical with those which followed its injection into a peripheral vein.

The clinical literature contains many references to a diuretic effect of sodium dehydrocholate in patients with edema associated with con-

11. Stewart, Cantarow and Morgan.[1c] Modell and Travell.[10]

gestive heart failure and other conditions accompanied by hepatic functional impairment. This diuresis has been explained on theoretical and speculative grounds, usually being attributed to improvement in hepatic function, with consequent restoration of water balance. Despite sporadic reference to the observation of swelling of the kidneys in experimental animals, we were unable to find any reference to a detailed morphologic study of the kidneys following the administration of this substance. It seems to us that the clinically and experimentally observed diuresis may be explained more rationally on the basis of the development of a renal tubular lesion, being similar in this respect to the diuresis which commonly occurs soon after the administration of uranium nitrate.

SUMMARY

The intravenous administration of sodium dehydrocholate in the cat and dog results in a severe renal lesion characterized by regressive and regenerative changes in the tubular epithelium. Changes following injection into the portal vein were similar to those which followed injection into a peripheral vein. Advanced grades of nitrogen retention were observed twenty-four hours after a single injection.

The process of regeneration was characterized by the development of atypical forms of renal epithelium which were more resistant than the original epithelium to the toxic effects of sodium dehydrocholate and which appeared to develop into mature forms morphologically indistinguishable from the original tubular cells.

The characteristic renal lesion was essentially the same in animals with and without biliary stasis which received injections although mitotic figures were much more numerous in the former.

There was an alteration in the distribution of stainable lipid, which extended into the cells of the Henle and the collecting tubules, similar to that described in cats with nephritis due to uranium and with biliary stasis.

These observations suggest that the clinically observed diuretic effect of sodium dehydrocholate may be dependent on the development of a renal tubular lesion and may be comparable to the diuresis that occurs soon after the administration of uranium salts. Although the renal changes may possibly represent a peculiarity of species, their consistent occurrence in both the cat and the dog following the administration of sodium dehydrocholate in ordinary therapeutic dosage renders the advisability of the clinical employment of this substance doubtful, at least until more evidence is at hand of its innocuousness for man.

Case Reports

DUPLICATION OF THE SPINAL CORD, WITH SPINA BIFIDA AND SYRINGOMYELIA

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Malformations of the spinal cord are of interest not only to the pathologist but to the embryologist, who from such arrests and aberrations of development may draw important conclusions as to the early stages of growth of the central nervous system. The present case is one of the rare instances of duplication of the lower segments of the spinal cord, and the anomaly does not belong to the large group of artefacts in which Van Gieson, somewhat radically, wanted to place most such malformations which had been reported prior to his time.[1] The case may be classified with the relatively few instances of duplication of the spinal cord which has its origin in a discrepancy of embryonic growth produced either, as the older theories explained, by lack of closure of the open neural tube and folding of its lateral walls or, as newer investigations suggest, by lack of fusion of the two separated tubes of the solid anlage of the lumbar segments into one central canal.

REPORT OF A CASE

History.—The spinal cord of a child, 5 months old, was obtained through the cooperation of Dr. Philip Kreuscher. Operation had been performed for the relief of spina bifida, and an attempt had been made to remove the meningocele. But an ascending infection of the urinary tract developed and pyelonephritis and death followed.

Anatomic and Histologic Report.—Grossly, the cervical segments of the spinal cord showed no abnormalities. At the middle of the thoracic region the spinal cord bulged. The posterior wall of the cord at this level was ruptured, and the opening led into a cavity which extended through approximately three segments. At the lower end of the dorsal segments the spinal cord was divided into two separate cords, which at the cauda equina were surrounded by thick scar tissue consisting of muscles and connective tissue (fig. 1).

Cervical Enlargement: Sections from this level showed a well developed spinal cord, which, however, was exceedingly flat. The anterior horns differed

From the Institute of Neurology and the Department of Pathology of Northwestern University Medical School and the Wesley Memorial Hospital.

1. Van Gieson, I.: New York M. J. **56**:336, 1892.

in size. The smaller contained fewer, more elongated and smaller neurons than the horn of the other side. The central canal was widened and lined with an inner row of large cylindric cells with cilia on the inner surface and an outer row of slender cells with long processes extending into the spinal cord (fig. 2). This type of lining of the central canal with similar primitive ependymal cells and supporting spongioblasts was observed throughout the whole spinal cord and in the halves of the duplication. Both the anterior and the posterior roots were present and contained myelinated fibers.

Upper Thoracic Segments: Sections from this level showed a microscopic picture similar to that already described. In the posterolateral column at one side there was an area of glial proliferation consisting in the peripheral portion of a loose meshwork of fibers and numerous glia cells; among them were adult astrocytes intermingled with more primitive, spongioblast-like forms and large cells without processes, the nuclei of which contained different stages of mitotic division (fig. 3). The center of this area was necrotic, and in some sections a central cavity (syrinx) had developed.

Midthoracic Segments: Sections from this level revealed a marked hydromyelia, which had compressed the spinal cord to such an extent that only a thin

Fig. 1.—Posterior surface of the spinal cord. The transverse lines *a*, *b* and *c* indicate the approximate level from which the microscopic sections were taken photographs of which appear in figures 4, 5 and 6, respectively.

wall of nerve tissue remained (fig. 4). In other sections the posterior wall of the cavity was ruptured (fig. 1). More caudal sections showed gradual division of the central canal into two portions and gradual separation of the spinal cord into three parts, set off by pia-arachnoid. The middle part showed no specific structure but contained only glia, while the lateral and larger parts possessed the structure of a small spinal cord, as described later. At this level the posterior wall of the central canal, which, like the canal in the other segments with hydromyelia, had been deprived of its cellular lining, showed a wartlike protrusion of proliferated glia tissue.

Lower Dorsal Segments: Sections from this level revealed that the spinal cord had been divided into halves, which formed mirror images and were turned at an angle of 90 degrees with their anterior fissures facing each other. In each small spinal cord a widened central canal was present, lined with primitive ependymal cells. In each cord the two anterior horns were separated, but the posterior horns had been united into one, from which a posterior root originated at about the middle of the lateral portion of the circumference (fig. 5). Only one anterior horn, the one situated more anteriorly, was well developed; it contained normal

neurons and sent out an anterior root. The other anterior horn was considerably smaller; it contained fewer and smaller neurons and did not send out axons toward the periphery. Both the anterior and the posterior commissure were well developed. Only the column of Clarke next the well developed anterior horn had normal ganglion cells. Occasionally, isolated ganglion cells could also be seen in the region of the opposite column of Clarke. The central canal of both halves was widened and lined with embryonic ependymal spongioblasts. The outer zone of marginal glia (Held) was rather wide and contained many large astrocytes and fewer oligodendroglia and microglia cells. Each spinal cord had a well

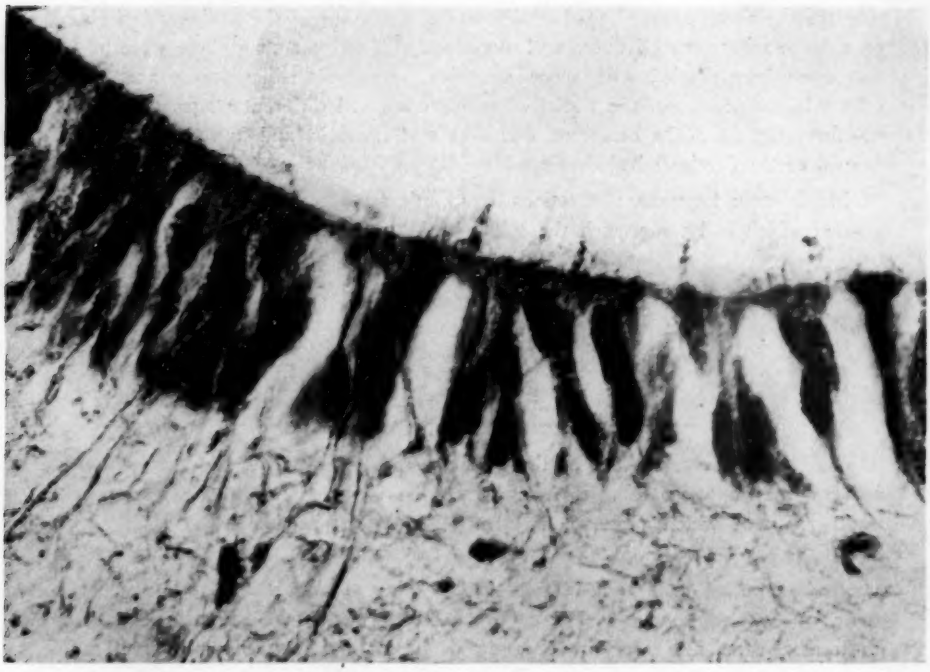

Fig. 2.—Photomicrograph of the lining of the central canal of an upper dorsal segment. Ciliated cells and an outer row of supportive spongioblasts which send out long processes toward the periphery are demonstrated. Davenport stain; Zeiss objective 3 mm., ocular 10 ×.

developed anterior fissure (pointing toward the midline) with separate blood vessels and pia-arachnoid. Furthermore, the two spinal cords were surrounded by a common sheath of connective tissue, with a large anterior spinal artery and vein.

Sacral Segments: Sections from this level revealed that the halves of the spinal cord were completely separated by dense masses of connective tissue, which also surrounded well myelinated nerve roots. In neither half was there a definite pattern of arrangement of the gray and white matter. The central canal was wide and lined as already described. Numerous small blood vessels were present,

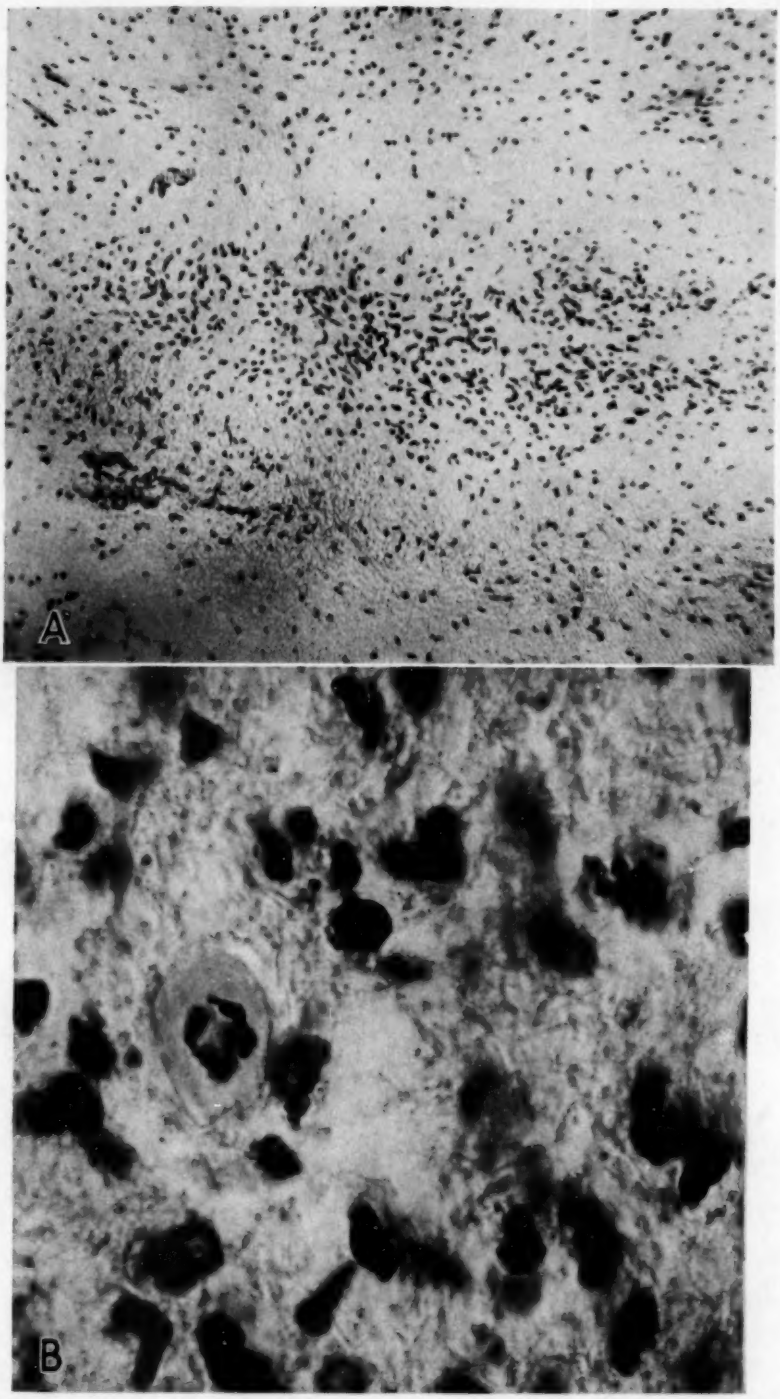

Fig. 3.—Photomicrograph of a section from an upper dorsal segment, showing (*A*) formation of a glioblastoma with beginning central necrosis (syringomyelia). (Van Gieson stain; Zeiss objective 10 ×, ocular 10 × and (*B*) mitotic figures in neoblastic glia cells in the same section (Zeiss objective 3 mm., ocular 10 ×).

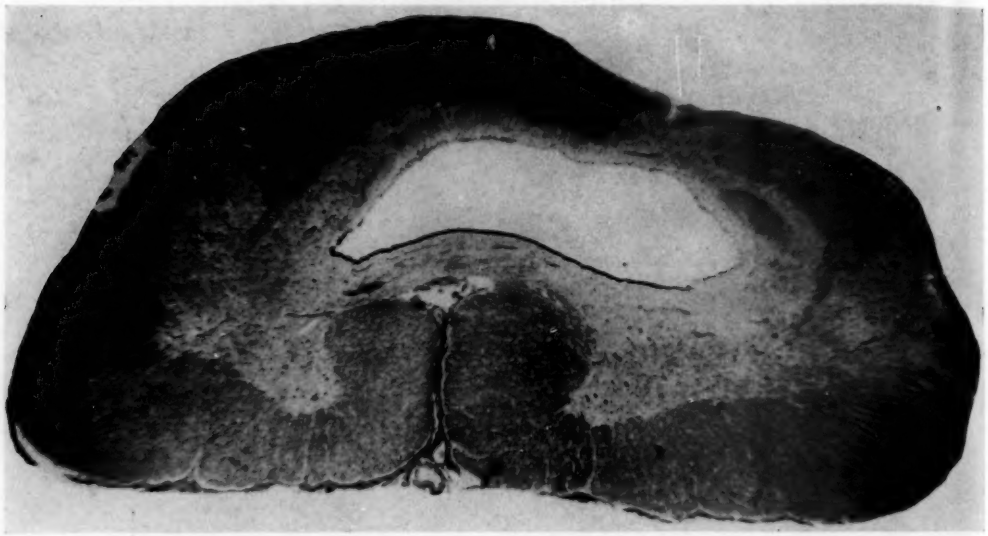

Fig. 4.—Transverse section through a middorsal segment, showing hydromyelia with destruction of the lining of the posterior wall of the central canal. Van Gieson stain; Zeiss objective 3 ×, ocular 10 ×; reduced approximately 8.5 per cent.

Fig. 5.—Transverse section through a lower dorsal segment, showing duplication of the spinal cord. To the right a posterior root is seen emerging from the posterior horn. Davenport stain; Zeiss objective 1.5 ×, ocular 6 ×.

surrounded by areas of proliferated glia, which in places showed beginning necrosis with the formation of a syrinx (fig. 6).

COMMENT

A review of the literature on duplication of the spinal cord published up to 1926 has been given in a previous paper.[2] Since then few cases of this malformation have been reported. Altschul [3] described such a duplication of the spinal cord in the upper dorsal segments of a child

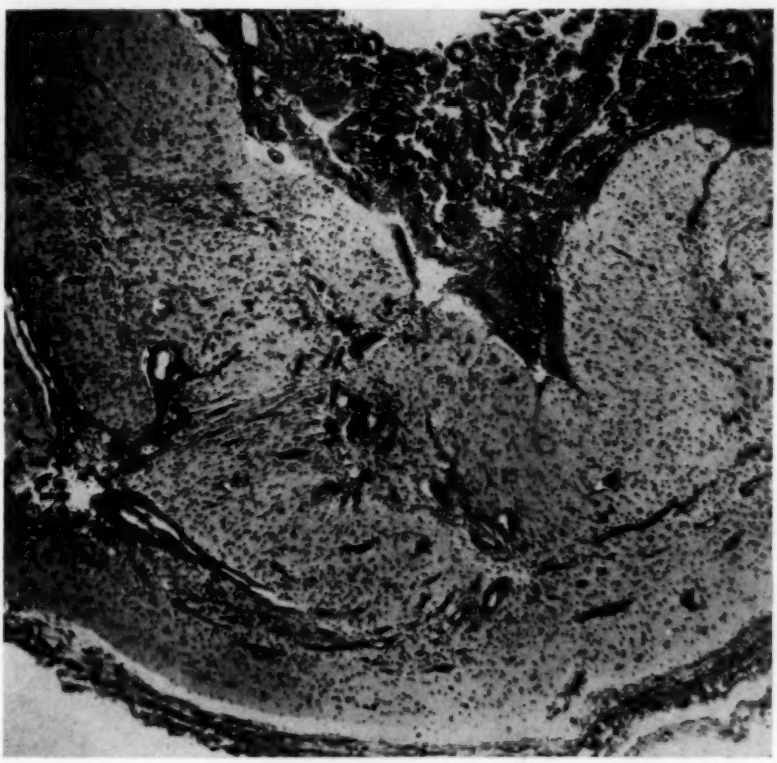

Fig. 6.—Transverse section through a sacral segment, showing marked increase in the number of blood vessels and thickening of the pia-arachnoid. Van Gieson stain; Zeiss objective 3 ×, ocular 6 ×.

9 months old. Each half contained a separate central canal, which was gradually united to the canal of the other half at the level of the twelfth dorsal segment, below which a normal spinal cord was again present. Unfortunately, no detailed description of the lining of the central canal was given, but it appears from the photomicrographs taken with low

2. Kraus, W. M., and Weil, A.: Rev. neurol. **2**:317 (Oct.) 1926.
3. Altschul, R.: Virchows Arch. f. path. Anat. **271**:45, 1929.

magnification that in this case, too, large cylindric cells were present. It seems that Altschul misinterpreted the French text of the publication of Kraus and Weil.[2] He cited them as "being inclined, on the basis of their own observation of an artificial duplication, to think that all malformations of the spinal cord are artefacts, according to the theory of Van Gieson." In reality, Kraus and Weil stated: "No case of duplication of the spinal cord as a whole has been reported in the literature which can be traced to a double embryonic anlage. . . . The duplications described had their origin in the formation of embryonic fissures, foldings of the medullary plate, separation of the spinal cord by new formations of the vertebral column and ingrowth of connective tissue or of tumors (dermoids)."

A second case of spina bifida combined with acrania and rachischisis was reported by Schenk.[4] His description corresponds exactly to that in the present case. The two separated spinal cords had been turned toward the midline at an angle of 90 degrees and represented mirror images. Each had the structure of a normal spinal cord with well developed horns of gray matter and a central canal. In a third publication von Sántha [5] described a duplication confined to the lumbar segments. Both spinal cords had the normal position of the cord in the adult, and the second, smaller, division was superimposed on the posterior part of the larger. If each spinal cord had not contained a separate central canal, one might have thought, judging from the drawings of sections of the lumbar segments, that perhaps one was dealing with an artefact, a pseudoheterotopia.

The present case is of interest on account of the manifold evidences of retardation of development. Unusual is the preservation of ciliated ependymal cells and supportive spongioblasts in a child 5 months old. Furthermore, the presence of mitotic figures in the nuclei of the foci of proliferated glia indicates that the embryonic tendency to growth had not yet been arrested or led into adult channels. The position of this center of growth close to the central canal is in accordance with the normal embryonic growth of the spinal cord, which starts from germinal centers close to the central canal and from which newly formed spongioblasts and neuroblasts migrate toward the periphery. The formation of a central cavity of necrosis within the foci of glial proliferation in the upper dorsal segments sheds an interesting light on the development of syringomyelia. It supports the prevalent theory that syringomyelia arises from the central necrosis of an intramedullary glioblastoma. This neoplasm may develop from embryonic rests of spongioblasts which remain close to the midline

4. Schenk, V. W. D.: Ztschr. f. d. ges. Neurol. u. Psychiat. **146**:369, 1933.

5. von Sántha, K.: Ztschr. f. d. ges. Neurol. u. Psychiat. **123**:753, 1930.

and posterior to the central canal in the upper dorsal and the lower cervical segments. The presence of mitotic figures and the active proliferation of glia cells with the formation of primitive spongioblasts indicate that in this case a real neoblastic formation was present, a glioblastoma, and not merely a reactive gliosis stimulated by the pressure atrophy of the spinal cord following the marked hydromyelia. The degree of hydromyelia must have been considerable in the segments below these foci of syringomyelia, because it produced such marked thinning of the substance of the spinal cord that the thin, bulging wall ruptured during careful removal of the cord. The marked overgrowth of blood vessels in the sacral segments and the surrounding gliosis may have been the first step toward the formation of a hemangioma, which occasionally is noted in this region. Besides, there was a tendency toward abnormal growth of the pia-arachnoid. Considerable thickening occurred throughout this membrane, which assumed massive proportions in the lower part of the sacral region and around the cauda equina.

Another interesting feature in this case is the development of the anterior and posterior horns of gray matter and their corresponding nerve roots in the duplicated segments. Though there were two anterior horns in each half, only the more anteriorly situated contained well developed neurons and gave rise to an anterior root. From the second, underdeveloped, anterior horn of gray matter no axons were seen streaming peripherally. In some sections there was the suggestion of two posterior horns in each half, but the one situated more posteriorly usually was atrophic. In most sections the two horns were combined, and only one posterior root arose from it, near the middle of the lateral surface of the cord. These observations are of considerable interest to the embryologist. They testify to the development of spinal nerve roots and muscle metameres independent of the development of the spinal cord. In this connection may be cited the case reported by Sokolansky,[6] who described the absence of the spinal cord in a fetus in the presence of well formed posterior spinal nerve roots and ganglions. In the present case, furthermore, only one well formed column of Clarke was present in each half of the duplicated cord. It was situated on the side of the exit of the posterior nerve root, i. e., in the anterior half of each duplication. The intersegmental nerve connections of each half of the spinal cord were well developed. There were an anterior and a posterior commissure containing myelinated fibers, and the intersegmental fiber tracts were well formed. With the exception of a rather wide zone of marginal glia, there was no abnormality in the formation of the posterior, lateral and anterior columns, which contained numerous myelinated fibers.

6. Sokolansky, G.: Arch. f. Psychiat. **92**:354, 1930.

Many theories have been advanced to explain such a duplication of the spinal cord associated with rachischisis. Riley has discussed all the theories in detail.[7] Most former investigators assumed that the whole spinal cord arises from an open neural tube, and they concluded, therefore, that failure of the tube to close and subsequent folding of the isolated lateral walls of the tube resulted in such a duplication. More recently, Holmdahl,[8] Ikeda [9] and others suggested that early in embryonic life the caudal part of the spinal cord develops not from an open tube but from a solid bundle of cells in which two or more cavities are formed. Later, the two tubes become confluent, and the united cavities form the central canal. Failure of such a fusion results in persistent duplication of the lower segments of the spinal cord; around each cavity nerve tissue forms a spinal cord, which is separated from its duplicate by ingrowing connective tissue. In the middorsal or the upper dorsal region the two separated central canals gradually become confluent, as was illustrated in Altschul's case and also in ours.

SUMMARY AND CONCLUSIONS

A case of duplication of the spinal cord beginning in the lower dorsal segments associated with spina bifida is described. Besides, marked hydromyelia of the middorsal segments, a central canal lined by ciliated ependymal cells and supportive spongioblasts and formation of a glioblastoma, with central necrosis and syringomyelia in the upper dorsal and the lower cervical segments, were present.

7. Riley, H. A.: J. Nerv. & Ment. Dis. **72**:1, 1930.
8. Holmdahl, D. E.: Morphol. Jahrb. **54**:333, 1925; **55**:112, 1925.
9. Ikeda, Y.: Ztschr. f. Anat. u. Entwcklngsgesch. **92**:380, 1930.

ARSENIC NECROSIS OF THE STOMACH AFTER INTRAVENOUS INJECTION OF NEOARSPHENAMINE

OSCAR O. CHRISTIANSON, M.D.,* CHICAGO

Among the more serious lesions occasionally produced by the intravenous administration of arsenic are profound changes of the hematopoietic tissues of the bone marrow, such as aplastic anemia, agranulocytosis and purpura haemorrhagica; hemorrhages of the brain, termed hemorrhagic encephalitis, and acute retrogressive and fatty changes of the liver. Hemorrhages, according to Petri,[1] are the commonest lesions observed post mortem in these cases. They occur in the brain, heart, pleurae, serosa, lungs, kidneys, mouth and lining of the gastro-intestinal tract.

A review[2] of the reports on 72 syphilitic patients whose deaths resulted from complications due to the intravenous administration of compounds of organic arsenic, yields the following conclusions: Fourteen died of aplastic anemia, 7 of agranulocytosis, 4 of purpura haemorrhagica, 4 of acute yellow atrophy of the liver, 2 of necrosis and hemorrhages of the kidneys, eighteen of hemorrhagic encephalitis and 25 of complications apparently due to arsenic therapy, but without characteristic changes in the viscera. In 38 cases there were no appreciable changes in the lining of the stomach or intestinal tract; in 23, petechial hemorrhages of the gastro-intestinal tract; in 8, similar changes of the stomach alone, and in 2, hemorrhages only of the lining of the small bowel. Herzog[3] published the only report of a case in which the stomach showed marked changes, consisting of extensive erosions, hemorrhages and edema of the lining and in which ulcerations were present in the large bowel. His patient had received eleven intravenous injections of neoarsphenamine, the last about one month before death.

According to these statements, edema and petechial hemorrhages of the lining of the stomach are the usual changes noted in cases of arsenic poisoning due to intravenous medication. The extensive necrosis, associated with edema and hemorrhages, described in the following report is rare.

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From the Henry Baird Favill Laboratory of St. Luke's Hospital.

1. Petri, E., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1930, vol. 10, p. 159.

2. These statements were compiled from forty-five references collected from the Quarterly Cumulative Index and the Quarterly Cumulative Index Medicus for the years 1917 to 1933, inclusive.

3. Herzog, G.: München. med. Wchnschr. **65**:29, 1918.

REPORT OF CASE

A white man aged 46 entered St. Luke's Hospital on July 18, 1934, because of bleeding from the gums for three days and general weakness. He had petechiae of the palate and buccal and pharyngeal mucosa and a purpuric eruption of the skin of the thighs and legs. The temperature was 100.2 F. The blood count showed 3,310,000 erythrocytes, 750 leukocytes and 3,300 platelets per cubic millimeter. The differential examination revealed 2 per cent band-shaped polymorphonuclears, 6 per cent eosinophils, 2 per cent monocytes, 90 per cent small and large lymphocytes and no mature polymorphonuclears. The bleeding time and coagulation time were fifteen and four minutes, respectively. The hemoglobin content was 58 per cent (Sahli). The urine was unchanged. The clinical diagnosis was agranulocytosis. Three blood transfusions and daily intramuscular injections of pentnucleotide and liver extract during ten days made no appreciable change. Death occurred on July 28.

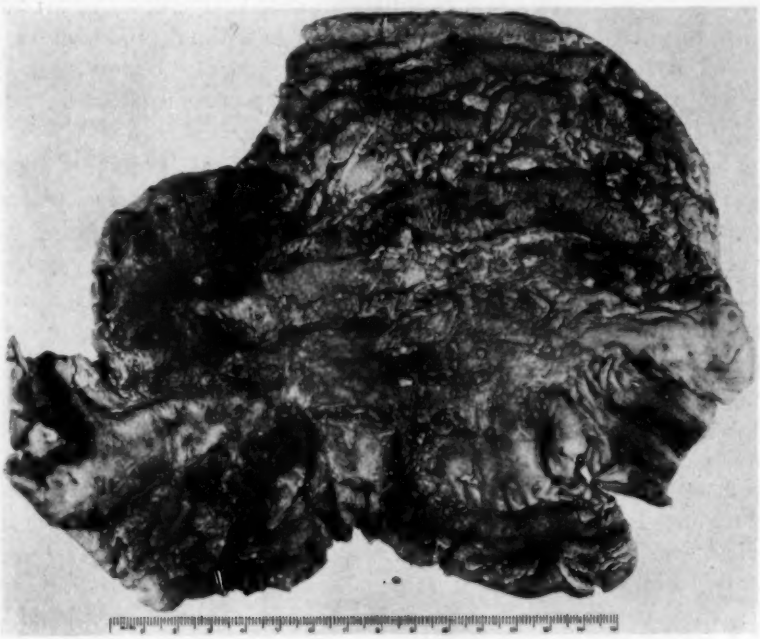
The patient had visited a public clinic in February because of weakness and mental changes. The serologic tests for syphilis were positive, and tests of the spinal fluid were negative. In 1922 a Wassermann test of the blood made at the same clinic was negative. During February and March 1934 the patient was given five intramuscular injections, each of 0.2 Gm., of bismuth subsalicylate at intervals of one week, and four intravenous injections, each of 3 Gm., of sodium iodide. For the next six weeks he was given weekly intravenous injections of neoarsphenamine, the average dose being 0.6 Gm., and weekly intramuscular injections of 0.2 Gm. of bismuth subsalicylate. From May 9 to June 6 the patient was not treated, and the Wassermann reaction of the blood was negative. On June 6 treatment was resumed, with four intramuscular injections of bismuth subsalicylate at intervals of one week and three intravenous injections of neoarsphenamine in the dosage mentioned. In all, 5.4 Gm. of neoarsphenamine was injected in approximately three months. He had no reaction until three days before entering the hospital—nineteen days after the last injection of neoarsphenamine.

The gross and microscopic postmortem examination revealed marked chemical (arsenic) pseudomembranous necrosis and hemorrhages of the lining of the stomach; signs of recent hemorrhage into the lumen of the stomach and the small and large bowel; acute ulcerative gingivitis; petechial hemorrhagic areas in the mucous membranes of the soft palate, pharynx, epicardium, lining of the inferior vena cava and lining of the large bowel; ecchymoses of the skin of the arms and legs; slight edema of the brain; central necrosis of the lobules and fatty changes of the liver; aplasia of the bone marrow; bronchopneumonia of the right lung; cloudy swelling of the myocardium, liver and kidneys, and marked anemia.

The lining of the stomach had large, markedly edematous rugae extending parallel to the long axis, varying from 0.5 to 2 cm. in width and projecting into the lumen about 1 cm. (fig.). These rugae and small, scattered, discrete portions of the lining of the stomach were covered by a gray-brown, firmly adherent pseudomembrane with many small and large red-brown hemorrhagic erosions and petechial hemorrhages. The mucosa beneath the membrane was necrotic. The gastric mucosa that was not covered by a membrane was dull, gray-red and edematous. The surfaces made by cutting the large rugae transversely had necrotic edematous mucosa, and the submucosa formed a wide irregular layer of red-brown tissue with many large hemorrhages. The edema of the tissues and the marked hemorrhages into the submucosa, although present in all portions of the stomach, were most marked in the rugae. There were no changes in the esophagus or the

duodenum. An eroded red-gray ridge on the lesser curvature, 2 cm. proximal to the pyloric ring, measured 5.5 by 3.5 by 1.5 cm. In the submucosa beneath was a large contracted blood clot. The serosa of the stomach seemed smooth.

Histologically, the mucosa and especially the submucosa of the stomach were markedly edematous. The surface of the lining was necrotic and covered by a pseudomembrane that was in places 1.5 mm. thick. It consisted of necrotic mucosa with slightly discernible structural details and a large amount of fibrin enmeshing desquamated cells, masses of red blood cells and brown blood pigment. The markedly edematous submucosa had extensive extravasations of red blood cells, dilated blood capillaries and deposits of hemosiderin. The walls of many small arterioles stained poorly, and the endothelial cells of many were swollen and



Corrosion, pseudomembranous necrosis and hemorrhages of the gastric mucosa.

loosened from the wall of the vessel. There were small collections of lymphocytes about a few arterioles in the mucosa and submucosa. The muscle and serosal layers had no noteworthy changes.

The liver and kidneys were analyzed by Dr. C. W. Muehlberger, the coroner's chemist. The liver contained 0.666 Gm. of arsenic, and the kidneys, 0.1255 Gm. The patient had received 5.4 Gm. of neoarsphenamine, or an equivalent of 1.946 Gm. of arsenic. Accordingly, the amount of arsenic recovered from these viscera was 40.36 per cent of the amount administered intravenously, presuming the arsenic medication was reported correctly. Considered in terms of unit weight, the liver had a slightly larger amount of arsenic than the kidneys. No mercury or bismuth was found in the viscera examined. Stained preparations of the necrotic mucosa showed a mixture of staphylococci, yeast cells and fusiform bacilli.

COMMENT

Various theories have been offered to explain the occasional corrosive-like changes, erosions, hemorrhages and edema of the mucosa of the gastro-intestinal tract following the oral or intravenous administration of various compounds of arsenic. Because of these changes in the mucosa, arsenic has been regarded as a corrosive poison. The usual changes of the lining of the gastro-intestinal tract of patients who have died from the effects of acute or chronic arsenic poisoning, however, are hyperemia, petechial hemorrhages and edema. Schaumberg, according to Merkel,[4] in 1893 reported such changes in 150 of 197 cases of acute arsenic poisoning. Pistorius [5] administered large doses of arsenous acid intravenously and orally to cats and dogs without producing corrosion of the lining of the gastro-intestinal tract. Unterberger and Boehm,[6] in similar experiments, produced pseudomembranes of the lining of the small intestine but not of the stomach.

The excretion of arsenic has been thought to be mainly by the mucosa of the gastro-intestinal tract. The hyperemia, edema, petechial hemorrhages and other changes following intravenous medication were explained according to that view. Lesser [7] in 1878 ligated the esophagus of a dog, then injected arsenous acid intravenously and subsequently noted arsenic in the gastric and intestinal contents. He concluded that arsenic is excreted by the lining of the gastro-intestinal tract.

Others have demonstrated that arsenic is excreted into the bile in large quantities. Kolls and Youmans [8] injected neoarsphenamine intravenously into twenty dogs. In three of these the common bile duct was ligated, and the bile was collected. It was found that approximately eight times as much arsenic was excreted in the bile as in the urine. Arsenic was noted in the stomach content only when bile was present. Bulmer [9] obtained the same results. He noted traces of arsenic in the intestinal contents of dogs with ligated bile ducts, but he considered that it was due to contamination. Within five minutes after injection, the liver contained the largest amount of arsenic, but later and for several days it contained less than the lungs, presumably because of the large amount excreted into the bile. According to Sollmann [10] also, most of

4. Merkel, Hermann, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 4, p. 294.

5. Pistorius, Hugo: Arch. f. exper. Path. u. Pharmakol. **16**:188, 1882.

6. Unterberger and Boehm, R.: Arch. f. exper. Path. u. Pharmakol. **2**:89, 1874.

7. Lesser, A.: Virchows Arch. f. path. Anat. **74**:133, 1878.

8. Kolls, A. C., and Youmans, J. B.: Bull. Johns Hopkins Hosp. **34**:181, 1923.

9. Bulmer, J. M. R.: J. Pharmacol. & Exper. Therap. **21**:301, 1923.

10. Sollmann, T.: A Manual of Pharmacology, Philadelphia, W. B. Saunders Company, 1926, p. 965.

the arsenic is excreted through the bile, the first 60 per cent rapidly and the remainder slowly.

Arsenic, therefore, does not act directly on the lining of the stomach or intestinal tract as a corrosive or irritant, but in toxic doses it produces a vasoparalysis and vasodilatation of the small arterioles and capillaries of the mucosa and submucosa. This vasoparalysis results from its toxic action on the innervation of the capillaries. Boehm, Unterberger and Pistorius were among the first to note the vasoparalytic action and subsequent marked drop in blood pressure when toxic doses of arsenous acid were administered orally or intravenously to dogs. The vasoparalysis caused marked circulatory stasis and sometimes produced thrombi. Following the vasodilatation, hemorrhages and marked exudation of plasma were noted. These changes, they stated, seriously impede the blood supply of the overlying mucosa. The mucosa becomes necrotic and together with the exudates and fibrin forms the pseudomembrane. The mucosa thus seems excoriated or corroded.

The patient whose case has been reported probably was sensitive to neoarsphenamine. The gross and microscopic changes noted were compatible with lesions caused by a primary vasoparalysis of the small blood vessels in the gastric mucosa and submucosa. There appears to have been delayed excretion of arsenic, because, according to chemical analyses, 40.36 per cent of the arsenic was recovered in the kidneys and liver thirty-one days after the last injection of neoarsphenamine.

The micro-organisms that were present in the necrotic gastric mucosa are believed to have been secondary invaders, similar to the flora commonly found in the saliva of the mouth.

SUMMARY

This report describes marked arsenic necrosis and hemorrhages of the lining of the stomach of a patient who had been treated for syphilis with intravenous injections of neoarsphenamine in moderate doses. Thirty-one days had elapsed since the last injection of neoarsphenamine.

Laboratory Methods and Technical Notes

THE APPLICATION OF THE GRAM STAIN TO PARAFFIN SECTIONS

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Although Christian Gram [1] originally devised his staining method for the demonstration of bacteria in tissues, it is doubtful if he recognized the existence of bacteria which were decolorized by this method. The use of a counterstain was a later introduction which led to the concept of gram-positive and gram-negative organisms (Conn [2]). At the present time the Gram stain is important to bacteriologists because it immediately provides a broad classification of bacteria and shows their morphology as well. Its usefulness, however, has been largely limited to smears. When the stain is applied to tissue sections the results are disappointing.

Weigert's [3] method for the staining of fibrin and gram-positive bacteria gives good histologic results and is still widely in use, but it does not stain gram-negative organisms. MacCallum [4] recommended a combination of Weigert's and Goodpasture's stains, which differentiate gram-positive and gram-negative bacteria. Other methods accomplishing the same purpose have been reported by Lillie,[5] Scudder and Lisa,[6] Brown and Brenn [7] and Rudnikoff and Stawsky.[8]

The use of trinitrophenol in some of these methods suggests that the failure of the usual Gram stain to give satisfactory histologic results may lie in the unsuitable concentration of hydrogen ions at which the stains are applied. Experiment justifies this assumption.

A series of paraffin sections of the same material containing both gram-positive and gram-negative bacteria was stained as follows:

Each section was brought through xylene and alcohol to water in the usual way. Gentian violet was applied for one minute, followed by compound solution of iodine for one minute, and the sections were decolorized with 95 per cent alcohol and then washed in water. Buffered solutions at p_H varying from 1 to 13 were applied for one minute. Dilute carbolfuchsin was added for one minute to the buffered solutions on the slide. The sections were differentiated and dehydrated rapidly in acetone, cleared in xylene and mounted in balsam.

From the Department of Bacteriology, McGill University.

1. Gram, C.: Fortschr. d. Med. **2**:185, 1884.
2. Conn, H. J.: Stain Technol. **5**:46, 1930.
3. Weigert, C.: Ztschr. f. wissensch. Mikr. **4**:512, 1887.
4. MacCallum, W. G.: J. A. M. A. **72**:193, 1919.
5. Lillie, R. D.: Arch. Path. **5**:828, 1928.
6. Scudder, S. A., and Lisa, J. R.: Stain Technol. **6**:51, 1931.
7. Brown, J. H., and Brenn, L.: Bull. Johns Hopkins Hosp. **48**:69, 1931.
8. Rudnikoff, I., and Stawsky, H.: Arch. Path. **19**:543, 1935.

At p_H 7 and above, the tissue as a whole was a diffuse red, the histologic character being difficult to make out, and no differentiation between gram-positive and gram-negative organisms being shown. Below p_H 7, the differentiation of bacteria and histologic structure became increasingly clear with increasing acidity until at a p_H between 2 and 3 the most satisfactory preparations were obtained. At p_H 2 and below, basic fuchsin itself becomes decolorized. Similarly, at p_H 2 and below, gram-positive organisms (except the acid-fast variety) lose the gentian violet, as can be demonstrated by washing in water and subsequently staining with basic fuchsin at p_H 3 or 4.

The experiment demonstrates that the Gram stain can be applied successfully to tissue sections if the p_H at which the basic fuchsin is employed is controlled. Buffered solutions are unnecessary. The commonly used Gram stain for smears can be applied successfully to sections if the section is treated with hundredth-normal hydrochloric acid for one minute before the application of the basic fuchsin.

As far as the staining reactions of the bacteria are concerned, this result might have been predicted from the work of Stearn and Stearn,[9] who found an iso-electric staining range for gram-positive bacteria in the neighborhood of p_H 2 to 3 and a somewhat wider range centering about p_H 5 for gram-negative bacteria.

The problem of securing satisfactory histologic detail simultaneously with good bacterial differentiation introduces the question of decolorizer. Churchman's [10] statement that the "ability to retain the dye when stained by the method of Gram is not a property of living cells in general but is almost entirely confined to yeasts and bacteria" must be regarded as more relatively than absolutely true. When alcohol is used as decolorizer, more or less of the violet is retained by the cell nuclei. As Lillie [8] pointed out, acetone is a more effective and more rapid decolorizer for tissue sections. Moreover, he compared the effects of alcohol and of acetone as decolorizers on smears of eighty-three different organisms. When discrepancies occurred, the results after the use of acetone were more often nearer to the accepted Gram reaction for the organism in question.

Lillie's contention as to the effectiveness of acetone as a nuclear decolorizer has been verified in the present study. The importance of the iodine might be mentioned, for, if it is omitted, even acetone fails to remove the violet from the nuclei. If iodine forms a precipitate with the gentian violet which is adsorbed on nuclear as well as on bacterial surfaces, this precipitate is removed by acetone from nuclei and gram-negative bacteria within ten seconds, but not from gram-positive bacteria. Evidence that this behavior may be related to lipoid substances is found in the observation that the myelin sheaths of nerve cells retain much of the violet after being washed with acetone following staining with gentian violet and iodine.

9. Stearn, A. E., and Stearn, E. W.: J. Bact. **9**:463, 479 and 491, 1924; **10**:13, 1925.

10. Churchman, J. W., in Jordan, E. O., and Falk, I. S.: Newer Knowledge of Bacteriology and Immunology, Chicago, University of Chicago Press, 1928, chap. 3, p. 24.

In order to improve histologic detail further a cytoplasmic stain may be added profitably. A number of these have been tried, including trinitrophenol, eosin, orange G, metanil yellow, acid yellow G. In general, these may be used either before or after the Gram procedure without markedly interfering with the bacterial and nuclear stains. The choice of cytoplasmic stain is governed by the need for a color value which gives maximum contrast between cytoplasm, bacteria and nuclei and at the same time is light enough to permit identification of bacteria when very few are present. For this purpose, trinitrophenol has been found most satisfactory.

The details of the procedure of staining which has given the best results with a variety of tissues follow:

Paraffin sections are brought through xylene and alcohol to water in the usual way.

1. Stain with carbol gentian violet for two minutes.
2. Drain but do not wash.
3. Apply iodine (I_2: KI : H_2O—1 : 2 : 300) for one minute.
4. Apply acetone until no more color is removed (about from ten to fifteen seconds).
5. Wash in water. Do not allow the section to dry.
6. Apply 0.05 per cent basic fuchsin in five hundredth-normal hydrochloric acid for three minutes.
7. Drain but do not wash.
8. Apply saturated aqueous trinitrophenol for from thirty seconds to one minute.
9. Wash in water.
10. Differentiate and dehydrate in acetone for from ten to fifteen seconds.
11. Clear in xylene.
12. Mount in balsam.

The gentian violet used is a product of the National Aniline and Chemical Company labeled "Gentian Violet (Crystal Violet)". Its dye content is 90 per cent. The color index number is 681. It has been certified by the Commission on Standardization of Biological Stains with certification number N.C. 14. The stain was prepared by triturating in a mortar 1 Gm. of gentian violet with 1 Gm. of phenol crystals. Ten cubic centimeters of absolute alcohol was then added. This stock solution was diluted ten times with distilled water, allowed to stand forty-eight hours and filtered before using.

This particular brand of dye is not essential to the method. Equally good results have been obtained using methyl violet 5 B Grubler and crystal violet Grubler.

The basic fuchsin employed is a product of Grubler. Further information about this dye is not available, nor is it known whether the dye is the chloride or the acetate. The important point in its preparation is that it is made up by dissolving 0.05 per cent of the dry dye in a solution having a p_H between 2 and 3. In fact, this is the essential feature of the entire procedure. Whether this p_H is obtained by the use of five hundredth-normal hydrochloric or tenth-

normal acetic acid or a buffered solution seems to be unimportant. This observation indicates that it is immaterial whether the basic fuchsin is a chloride or an acetate. Several samples of basic fuchsin of unknown origin have given almost equally good results. Safranin O Grubler has also been employed successfully at p_H 2.5, but cleaner histologic detail is obtained by the use of basic fuchsin. The most suitable concentration seems to be 0.05 per cent.

The use of a staining rack and dropping bottles rather than staining jars is recommended since it permits the use of uncontaminated reagents.

Preliminary fixation of tissue can be accomplished by the common fixatives; formaldehyde solution, U. S. P. (1:10), Zenker's fluid, Zenker's fluid plus dilute solution of formaldehyde or Bouin's fixative can be used with success. Better histologic detail seems to be obtained by the use of Zenker's fixative without acetic acid.

When viewed under the low power of the microscope the tissue is lightly stained. Gram-positive bacteria are deep violet and easily identified with the low power lens. Where cellular exudation is not too abundant, the deep red gram-negative bacteria can also be seen under the low power lens in contrast to the lighter red nuclei. Under oil immersion both types are sharply differentiated.

Nuclear chromatin stains red; cytoplasm, faint yellow. The nuclei of nerve cells show differentiation of nucleoli and Nissl bodies. Axons are unstained. Myelin sheaths are violet. Edema fluid, fibrin and the fibers of connective tissue are pale pink. Erythrocytes are yellow.

Gram-positive bacteria are deep violet. Staphylococci, streptococci, the mycelia of actinomycetes and the vegetative forms of spore-bearing species are solidly stained. Diphtheria bacilli show barred and granular forms. Human tubercle bacilli are less deeply stained than other gram-positive organisms and show distinct beading.

Gram-negative bacteria are uniformly red. The clubs of actinomycetes are also red and contrast sharply with the gram-positive mycelium.

The chief advantage of this stain is that it not only provides simultaneously good histologic and bacterial differentiation but stains all bacteria that may be present. This is particularly useful in the study of tuberculous tissue where very young tubercle bacilli may not be acid-fast, and secondary invaders are easily identified.

SUMMARY

A modification of the Gram stain applicable to paraffin sections is described. The essential feature of the procedure is the use of basic fuchsin at a p_H of from 2 to 3. Good histologic differentiation as well as simultaneous staining of gram-positive and gram-negative bacteria is obtained.

FORCEPS AND RETRACTORS MADE FROM SAFETY-PINS

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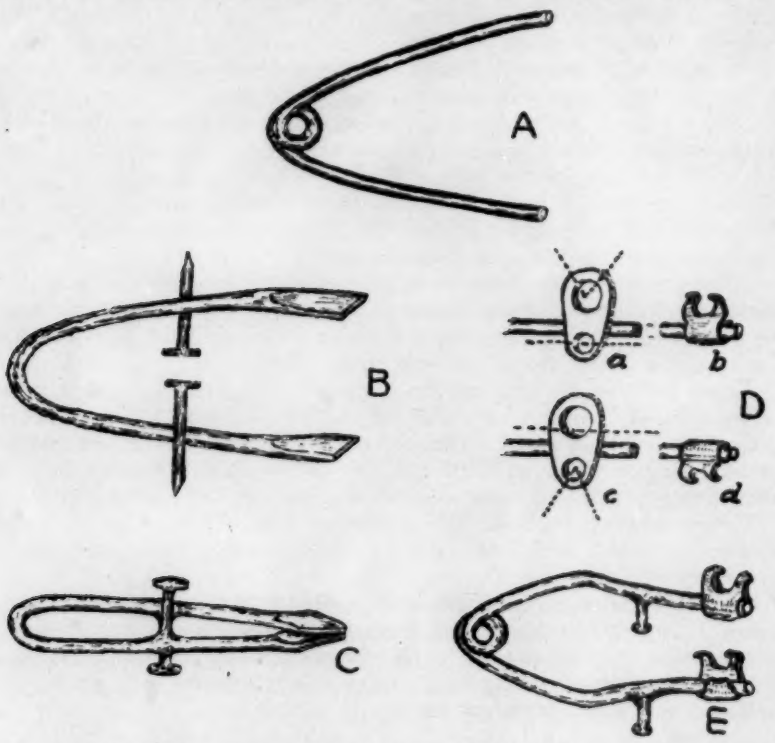
In the absence of sufficiently small yet accurate forceps, safety-pins may be converted into these instruments with little effort and no expense.

The head of a no. 3 safety-pin, together with a corresponding amount of the pointed end, is clipped off (figure, *A*). The spiral in the spring is converted into



Drawings illustrating conversion of a safety-pin into a forceps and a retractor.

a simple loop by appropriate bending, and the ends of the pin are hammered flat. Small nails of the size indicated (no. 18 wire nails ¾ inch [1.9 cm.] long) are soldered in position as shown in the figure, *B*. The projecting points of the nails are clipped off, and the cut ends as well as the excess solder are filed smooth. A small amount of solder is spread on the inner aspect of the flattened ends, and the two limbs of the forceps are approximated to the desired position. The jaws of the forceps are then dressed with a breaker-point file so that they will grasp a hair tenaciously (figure, *C*). The tension of the jaws can be increased by filling the loop spring with solder.

From the Institute of Pathology of Western Pennsylvania Hospital; Dr. Ralph Mellon, director.

A second very useful instrument made by modifying a safety-pin is a self-retaining retractor. For this purpose soldering lugs [1] of the size and shape indicated are employed. Depending on which end of these lugs is used, large-pronged (figure, *Db*) or small-pronged (figure, *Dd*) retractors are fashioned. Cuts are made into the lugs as shown by the broken lines in the figure, *Da* or *c*. These cut lugs are then soldered to the limbs of the safety-pin (figure *Db* or *Dd*, also *E*). The limbs of the retractor and the prongs are bent to give the desired tension. Wire brads are soldered to the limbs of the retractor to facilitate handling. The projecting points of the brads are clipped off, and the joints are filed smooth (figure, *E*).

1. Soldering lugs are obtainable in radio supply stores.

General Review

ETIOLOGY OF AGRANULOCYTOSIS

FREDERICK STENN, M.D.
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Though agranulocytosis owes its first accurate description to Brown and Ophüls, who reported a case in 1902, there exists information which indicates that this disease was possibly known a century ago and perhaps earlier than that. The blood count and the differential smear were available to physicians hardly much before the opening of the twentieth century, and thus a positive diagnosis of this disease entity was impossible. However, there are clearly described cases of a symptom picture which intimately parallels the modern conception of agranulocytosis, a fact appreciated in 1931 by Pepper. Almost twenty-three hundred years ago Hippocrates recognized a rapidly fatal pharyngeal disease characterized by gangrene with overwhelming symptoms. Celsus and Aretaeus noted the throat with its black eschar; Caelius Aurelianus and Aetius referred to the rare "synanche," the phlegmonous state of strangling of the throat, and Avicenna and Albucasis alluded to it in their memoirs. After their writings were published various names were applied to this condition, and among the common ones were ulcus syriacum ou egyptiacum, carbunculus anginosus morbus puerorum, *garotillo,* morbus suffocans, morbus strangulatorius, *ulcère gangréneux, mal de gorge gangréneux,* pharyngitis acuta infectiosa phlegmonosa and angina maligna.

In 1857 Adolphe Gubler described the case of a maid who became suddenly ill with a violent sore throat, followed by extensive gangrene of the pharynx, which terminated fatally. In 1859 Fernie became interested in the new disease to which his groom succumbed with surprising rapidity. In 1860 Musset reported a similar case but with recovery. And in 1861 Trousseau wrote: "Besides secondary gangrene there is a primary gangrene that should be regarded as a disease having as its fundamental character necrosis of the mucous membrane of the pharynx and sometimes necrosis of the cheeks and lips," which is "unrelated to any preceding disease, unassociated with epidemics of diphtheria, attacking healthy vigorous subjects without cause and often producing death with variable rapidity." The entity of putrid sore

From the Department of Pathology, the University of Chicago.

throat (angina putris) was defined in 1880 by Mackenzie in his treatise entitled "Diseases of the Pharynx, Larynx, and Trachea," as a "primitive gangrene of the pharyngeal mucous membrane, constituting an infection per se, . . . originating independently of any other malady, such as diphtheria, scarlet fever, etc.," always appearing "to be the result of blood poisoning" and commencing "as a severe inflammation which quickly leads to gangrene," the patient suffering from foul breath and extreme prostration and dying in syncope. Of his 5 patients only 2 recovered. It is interesting that Mackenzie observed that "putrid sore throat is only a local manifestation of a profound blood poisoning" and that it has its greatest occurrence "in physicians, nurses, and students," facts that are accepted today.

Much of the literature on putrid sore throat, otherwise called acute infectious phlegmon of the pharynx before 1900, referred to the 4 case reports of Senator, who in 1888 called attention to a "little recognized disease neglected clinically and concerning itself with a gangrenous and often fatal illness." Again, in 1889, Maurin undertook a detailed study of "l'angine gangréneuse primitive," collecting reports of 10 cases 4 of which were fatal. His observations agreed with those of Blumenau, who in 1896 declared that the disease appears most frequently among adults, producing a circumscribed or a diffuse form of gangrene in the throat, beginning with general malaise, depression, severe chills with high fever, severe pain in the throat, headache, prostration and often hemorrhages in the nose and throat and terminating with death due to septic poisoning.

However, the earliest accurate report of agranulocytosis was submitted in 1902 by Brown and Ophüls, who described the case of a mother aged 29. Three weeks after operative repair of the vagina and cervix there developed a chill, a temperature of 103 F. and a pulse rate of 112, and the patient complained of sore throat. The white blood cells numbered 1,200, with 1 per cent polymorphonuclears. The day before death the leukocyte count fell to 260. The authors entitled the disease acute primary infectious pharyngitis.

Two years later Schwartz described the case of a 9 year old boy with an abscess of the kidney which ruptured into the urinary tract. The leukocyte count was 600; no neutrophils were present.

In 1907 Türk treated a 45 year old woman who was suffering from staphylococcic sepsis and had chills, headache and diarrhea. The tonsils were covered with white exudate. After spending a whole day and night searching over a blood smear he was astonished at his inability to find a single neutrophil.

Baldridge and Needles found in the records of the University Hospital, of Iowa City, a report of the case of a girl aged 8 years who

died in 1910 of typical agranulocytosis. In the same year Leale reported a case occurring in an infant suffering from marasmus and furunculosis. This case will be referred to later under the title cyclic agranulocytosis.

In 1912 Stursberg reported the case of a man aged 41 with osteomyelitis of one arm who bled from the nose and mouth and complained of oral pain and dysphagia. He died shortly after the leukocyte count fell to 900, with complete absence of granulocytes.

The study of the disease received its greatest impulse and widespread recognition in 1922 after Werner Schultz had reported a group of cases in women between the ages of 18 and 65 years, all of whom died. The clinical course lasted for three or four days in some instances and for one or two weeks in others. The illness began with high fever, with or without icterus, and all the patients showed necrotizing processes in the tonsils, pharynx, tongue, larynx, uvula, soft palate or gums. One patient showed gangrenous colpitis. There was no generalized lymphadenopathy or evident hemorrhagic diathesis. The highest leukocyte count was 1,800, and the blood smear showed only lymphocytes and monocytes, with occasional neutrophils. The red blood cell and the platelet count were normal.

Rapidly the medical world became aware of agranulocytosis and articles were published by Leon, Friedemann, Bantz, David, Ehrmann and Preuss, Elkeles, Feer, Lauter and Zadek, in Germany; Lovett, Hill, Hunter, Cannon, Skiles, Hart and Piette in the United States; Flandin, Mouzon, Roch and Mozer in France; Alagna and Gamma in Italy, and Pelnář in Czechoslovakia. Whether this sudden prominence of agranulocytic angina was due to the watchfulness of the physicians for the condition or to an actual outbreak of the disease is difficult to conclude. Certainly before 1922 the disease was seen rarely. Its frequency after that year has been attributed by some to the extensive therapeutic use of arsphenamine, gold, bismuth or aminopyrine; by some to factors in civilized life that are little understood and by others to a spontaneous outbreak, like a severe epidemic of influenza.

INCIDENCE AND PREDISPOSING ETIOLOGIC FACTORS

Many cases reported in the literature as instances of agranulocytosis were confused with those of aplastic anemia, aleukemic leukemia, overwhelming sepsis and other diseases; so the number of cases has been somewhat exaggerated, though the fact is to be heeded that this disease has been overlooked until recently and that probably its great incidence is due to its better recognition. Today the United States has the highest incidence; according to the Department of Vital Statistics at Washington, 1,981 deaths were reported in 1931, 1932, 1933 and 1934, with

the greatest frequency in California, New York, Illinois and Pennsylvania. Roberts and Kracke expressed the belief that the actual incidence reached many thousands. Germany and Austria, where the first reports

TABLE 1.—*Deaths in the United States from Agranulocytosis* *

1931	1932	1933	1934	Total
421	450	572	588	1,081

Data supplied by the Department of Vital Statistics, Washington, D. C.

TABLE 2.—*Incidence of Agranulocytosis in the United States Between 1931 and 1933* *

	Agranulocytosis			Agranulocytic Angina		
	1933	1932	1931	1933	1932	1931
United States	82	84	90	490	366	325
Alabama	..	1	1	6	3	2
Arizona	1	..	..	1	4	..
Arkansas	..	..	..	2	2	4
California	3	6	5	40	16	29
Colorado	..	2	..	4	5	2
Connecticut	2	4	2	9	9	8
Delaware	..	..	..	..	1	2
District of Columbia	1	..	..	3	6	1
Florida	2	2	2	5	2	..
Georgia	2	2	8	6	2	4
Idaho	..	..	1	1	1	1
Illinois	6	8	10	41	28	24
Indiana	2	2	..	9	7	5
Iowa	3	3	..	8	12	11
Kansas	2	3	1	8	4	5
Kentucky	5	3	1	6	2	1
Louisiana	..	2	4	4	9	8
Maine	..	..	1	2	..	..
Maryland	3	..	1	10	2	5
Massachusetts	2	2	6	31	15	14
Michigan	4	5	8	12	23	17
Minnesota	1	1	3	10	9	9
Mississippi	1	..	1	..	..	1
Missouri	2	1	4	9	9	14
Montana	..	1	1	3	1	3
Nebraska	1	4	3	11	10	5
Nevada	..	..	..	..	..	..
New Hampshire	..	..	..	1	..	..
New Jersey	2	4	3	24	18	15
New Mexico	..	..	..	..	..	..
New York	6	3	9	94	74	71
North Carolina	2	..	..	4	6	2
North Dakota	2	1	1	..	1	1
Ohio	5	6	2	15	10	16
Oklahoma	3	1	..	2	6	3
Oregon	..	1	..	4	2	1
Pennsylvania	6	3	4	40	23	15
Rhode Island	1	2	1	5	1	2
South Carolina	..	2	..	4	3	..
South Dakota	..	..	..	..	1	..
Tennessee	3	..	3	3	5	5
Texas	5	2	4	14	6	6
Utah	..	..	..	2	1	..
Vermont	..	..	..	..	1	..
Virginia	2	2	1	12	8	4
Washington	..	1	1	9	5	2
West Virginia	1	1	1	5	3	2
Wisconsin	1	2	3	10	11	5
Wyoming	..	1	..	..	..	..
Alaska	..	..	..	..	..	..
Hawaii	..	..	..	..	..	..
Puerto Rico	..	..	..	..	..	..

* The terms agranulocytosis and agranulocytic angina are headings under which physicians reported the disease. Data published by the United States Bureau of the Census, Washington, D. C.

of this disease were issued, rank second, with approximately 400 cases since 1922. Before 1930 in England and Wales the disease was almost unknown, but for the succeeding five years, as noted by Percy Stocks, medical statistics officer in London, there have been reports of 83 fatal cases and 7 recoveries. In France there have been reported about 100 cases and half that number in Italy. Reports are becoming numerous in the Scandinavian countries, especially Denmark, but Plum has claimed that the incidence there is diminishing rapidly following restriction of the therapeutic use of aminopyrine. Cases are only occasional in Russia, Poland, Egypt, Syria and Jerusalem and rare in China, Japan, Netherlands Indies, South Africa and Spain.

TABLE 3.—*Registered Deaths in England and Wales to the End of 1934 Attributed to Agranulocytosis or Agranulocytic Angina Alone or Associated with Other Causes* *

Age, Years	1930		1931		1932		1933		1934		Total	
	M	F	M	F	M	F	M	F	M	F	M	F
0– 4	..	..	..	..	..	..	..	2	..	..	..	2
5– 9	..	..	..	..	..	..	..	1	..	..	..	1
10–14	..	..	..	..	..	..	..	1	..	..	..	1
15–19	..	..	..	..	..	1	1	2	2	2	3	5
20–24	..	..	..	..	1	..	1	1	2	..	4	1
25–29	..	..	..	1	..	..	..	2	1	3	1	6
30–34	..	1	..	..	..	..	..	..	..	2	..	3
35–39	..	..	..	1	..	1	1	..	..	4	1	6
40–44	..	..	..	..	..	..	..	..	1	..	1	..
45–49	..	..	1	..	1	1	1	3	1	2	4	6
50–54	..	1	..	..	..	..	..	4	1	1	1	6
55–59	..	..	..	..	..	1	..	2	2	3	2	6
60–64	..	..	..	..	..	..	..	3	1	2	1	5
65–69	..	..	..	..	..	..	1	3	1	2	2	5
70–74	..	..	..	..	..	..	..	1	..	4	..	5
75–79	..	..	..	..	..	..	..	1	1	..	1	1
80–84	..	..	..	..	..	..	..	..	..	1	..	1
85–	..	..	..	..	..	..	..	..	..	..	..	..
Totals		2	1	2	2	4	5	26	13	26	21	60

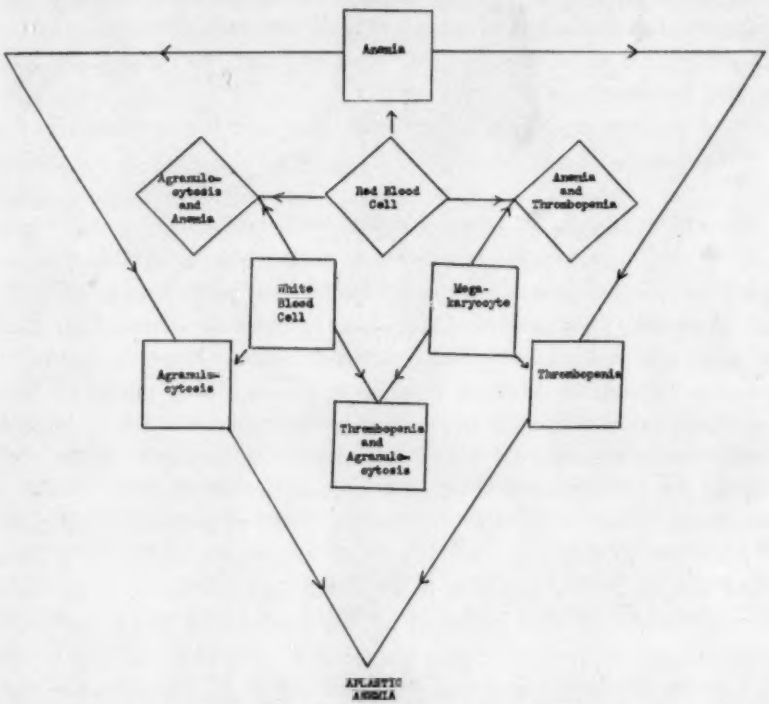
* No deaths were reported before 1930. Data supplied by the General Register Office, London.

The prominent incidence in women is a striking feature of this disease. Hueper found an incidence of 77.5 per cent in women, and Kastlin, of 78 per cent in women and 22 per cent in men. In England and Wales, according to Percy Stocks, the proportion is 3 females to 1 male, this ratio holding roughly true for most of the statistical data, though Gordon's figures showed 68.9 per cent females and 31.1 per cent males, and Kracke and Parker reported 310 women and 106 men.

The age of onset varies from 12 to 90 years, being most frequently between the ages of 40 and 60 years. Kastlin found that the average age for women was 46 years and that for men 29 years. Lichtenstein found the greatest occurrence between 40 and 50 years; Plum, between

50 and 60. Ridpath noted that in 80 per cent of all cases reported in women the disease has developed within the menstrual age, under 45 years, and that the symptoms have occurred one or two days after the onset of catamenia. In most of the cases reported in children the condition either has fallen into the category of aplastic anemia or has been precipitated by severe sepsis or the taking of a drug.

Seldom encountered in the Negro and yellow races, agranulocytosis is confined to Caucasians. The rarity of cases in Negroes was observed by Kracke and Parker, who stated that over a five year period at the



Bone marrow insufficiency. A schematic chart illustrating the interrelationships of anemia, thrombopenia, agranulocytosis and aplastic anemia.

Emory University Division of the Atlantic City Hospital, which has an annual admission of 75,000 Negroes, not a single case of idiopathic agranulocytosis was seen. No nationality is exempt.

Persons with moderate means and wealthy persons are more often attacked than the poor. This difference in social status may be only apparent, for those in comfortable circumstances are more likely to seek good medical advice early. Reports from the various charity hospitals reveal the infrequent occurrence. Dr. Karl Meyer stated that at the Cook County Hospital, Chicago, 9 cases of agranulocytosis

occurred between the years 1922 and 1935, only a few of them being of the idiopathic type. A study of the occupations concerned shows that the housewife is most frequently affected, then the physician, the nurse, the maid in the hospital, the medical student, the hospital orderly and the laboratory technician and finally the physician's relatives and the school teacher. The farmer, business man, clerk, tailor, dentist and others are less likely to be subject to the disease. Kracke and Parker emphasized its occurrence "fifty times more frequently in physicians than lawyers, and 200 times more frequently in nurses than in female school teachers." This peculiar tendency to affect those engaged about a hospital has been appreciated by Stellhorn and Amolsch, Harkins, Conner and his associates, Hinton, Sydenstricker, Fitz-Hugh and Comroe and Kracke.

Most authors have expressed the opinion that the seasonal incidence is unimportant, though Lichtenstein has observed most of his cases in winter.

No epidemiologic factors have been observed.

Only rare case reports mention any congenital or familial tendency. Wolff saw two sisters who took ill at one time with angina; a brother had agranulocytosis and a sister had myeloid leukemia. Hart and Strasser each observed the disease in two sisters. Roberts reported the case of a woman who died of myeloid leukemia. Her son had a leukocyte count of 3,500, and her sister became ill with agranulocytosis. Burcky noted the case of a girl who had a leukocyte count of 3,800, with 12 per cent granulocytes, following a sore throat from which she recovered. Ten months later her mother died of typical agranulocytosis.

The theory that a tendency toward leukopenia exists in a certain proportion of society and that it may be a decisive factor in precipitating this disease process is based on the analysis of large numbers of blood counts. Feer studied the case records of 29,498 patients between 1915 and 1925 and found that 193 had leukocyte counts below 3,000. In a study of 8,000 case records of patients seen in private practice in the South, Roberts and Kracke noted that one fourth of the patients and one half of the women between 40 and 60 years of age suffered from mild granulopenia. Mettier and Olsan stated that at the University of California Hospital 11.6 per cent of 10,000 case records from 1920 to 1931 revealed that the patients had leukopenia; 51.4 per cent of the patients with leukopenia were women, and 47.6 per cent were men. Despite this wide statistical discrepancy, these data teach that chronic leukopenia exists and that a leukopenic predisposition when mild, according to Cabot, Roberts and Kracke and Rosenthal, leads to vague symptoms, such as chronic fatigue, malaise, anorexia, neurasthenia, psychosis and exhaustion. When it is more severe granulopenia

is succeeded by the more drastic symptoms of agranulocytosis, as suggested by Roberts and Kracke. Doan observed that when infection develops in a person with chronic leukopenia, leukocytosis results and produces a response in the bone marrow; but in those persons who show symptoms of malaise and fatigue, with relative lymphocytosis, absolute neutropenia and a shift to the left, infection produces a more severe leukopenia and renders the myeloid tissue insufficient. Hueber studied 79 patients with agranulocytosis, 25 of whom exhibited fatigue extending for from four weeks to one year preceding the attack. These data suggest that a person with chronic leukopenia is particularly likely to have an acute attack of agranulocytosis.

Inquiry into the previous history of patients with this disease gives rise to numerous suggestions, but no single factor is constantly present. In Hueber's review of 79 cases, 49 patients had recently had injuries, operations or infections. Kastlin's review of 43 cases showed 27 with no history of any previous infection, while in the others there was a history of typhus, tuberculosis, syphilis, pneumonia, anemia, infection or operative procedure. Zetterqvist, Babbitt and Fitz-Hugh, Ridpath, Reznikoff, Hanzlik, Kracke and others reported cases in which the disease was precipitated by the extraction of teeth. In other cases it has followed a major operative procedure, such as thyroidectomy, or a fracture. Not infrequently the attack begins after a debilitating disease, especially influenza, as pointed out by Hirsch, Korach, Ottenheimer, Roberts and Kracke and others. Continued exhaustive states, toil, worry, asthenia and senile states in asthenic women have been mentioned as possible factors, in addition to arthritis and treatment for pyorrhea. Prolonged anemia has been stated to lead to dysfunction of the myelocytic tissue. Exposures of the skin to ultraviolet or infra-red rays, sunlight and x-rays are listed as factors. Some writers have blamed dietetic "obesity cures."

BACTERIOLOGY

No bacterium, group of bacteria, toxin or filtrable virus has been demonstrated to be the causative factor of agranulocytosis. The investigations of Schultz, Friedemann, Licht and Hartmann, Zetterqvist, Roberts and Kracke, Harkins and others have shown that these factors are secondary. Examination of the lesions of the throat, gastro-intestinal tract, vagina, skin or some other location has consistently shown the presence of numerous organisms: Staphylococcus aureus, Staphylococcus albus, Streptococcus viridans, Streptococcus haemolyticus, Vincent's spirochetes and fusiform bacilli, Bacillus diphtheriae, diphtheroid forms, Bacillus pyocyaneus and various types of spirilla and pneumococci, such as are found in ulcerative processes of many diseases. Werner Schultz injected into rabbits tonsillar tissue of patients dying of

agranulocytosis; Weihmuller injected secretions from the throat intraperitoneally into guinea-pigs, and Lichtenstein performed similar experiments, with negative results in each case. In like manner, blood culture has proved fruitless. The organisms isolated have been Str. haemolyticus, Str. viridans, Staph. aureus, Staph. albus, Friedländer's bacillus, pneumococci of types I to IV, B. pyocyaneus, Bacillus typhosus, Bacillus paratyphosus, Bacillus coli, Vincent's organisms, malarial parasites, B. diphtheriae, meningococci, Streptothrix and others. In their review of the literature Kracke and Parker found reports of 74 blood cultures that gave positive results, and in 395 instances either the cultures gave negative results or the results were not mentioned. The cultures gave positive results in 75 per cent of the cases in which they were taken, and the streptococcus was the commonest invader. Stocke noted that in only 23 per cent of 88 cases did the blood cultures show positive results, and in many of these the cultures were made post mortem. In Lichtenstein's 27 cases 13 of the blood cultures showed negative results, and 4 showed Str. haemolyticus. In Kastlin's review of 43 cases 9 blood cultures gave positive results, the organisms isolated being Str. haemolyticus, Staphylococcus, B. pyocyaneus and B. coli. Many patients die without having any organisms demonstrable in the blood.

Failure to produce the disease experimentally was reported by Garrod and Williams, who injected intravenously into rabbits and intraperitoneally into a guinea-pig a sample of blood of a patient dying of agranulocytosis. Schultz and Jacobowitz used rabbits; Licht and Hartmann, rabbits and white mice; Weihmuller, guinea-pigs, and Bix, guinea-pigs and white mice; and all failed to precipitate the disease. Roberts and Kracke fared similarly after giving rabbits and guinea-pigs intravenously, subcutaneously and orally Str. haemolyticus obtained by culture of the blood of a patient dying of the disease.

Some investigators, however, have obtained a decided leukopenia experimentally. Greer inoculated a guinea-pig with gram-negative bacilli obtained from a patient's blood and necrotic tissue from a patient's mouth and succeeded in obtaining ulceration of the gastro-intestinal tract, oral cavity, uvula, vagina, cervix and rectum; bronchopneumonia; submural and subpericardial hemorrhages, and depression of leukopoiesis. Schattenberg and Harris produced depression of the leukocyte and granulocyte count in rabbits with Staph. aureus isolated from the blood of a patient and with the toxins of Bacillus enteritidis, Str. haemolyticus and Bacillus Welchii isolated from the stool of a patient. Lichtenstein injected intravenously into each of 6 rabbits 1,000,000,000 streptococci obtained in pure culture from a patient's blood and produced marked leukopenia. He expressed the belief that the streptococci have a specific effect on the bone marrow. B. pyocyaneus has been

thought by some to be a possible etiologic agent. In 1924 Beatrice Lovett cultured this organism from the throat and the vagina of a patient dying of the disease and on injecting it into a guinea-pig obtained mild leukopenia and neutropenia. Skiles, Linthicum, Rose and Houser, Kastlin and others have found it to be an organism common in this disease. Friedemann obtained it from the heart, liver, and spleen and once from the blood, and Stillman reported it in the blood of 2 patients at autopsy. That B. pyocyaneus liberates a powerful leukocidin was shown in 1889 by Gheorghiewsky, who injected B. pyocyaneus into the peritoneal cavity of the guinea-pig and found marked degenerative and lytic changes in the neutrophils contained in the exudate. Yet Kracke was unable to reproduce the disease after injecting into animals B. pyocyaneus cultured from material from ulcers of the mouth and blood in 2 cases, and similar failures have been reported by others.

Fried and Dameshek observed that a relatively small intravenous dose of Salmonella suipestifer produced slight leukopenia; a large dose produced greater leukopenia, and an overwhelming dose produced areas of necrosis in the bone marrow.

Meyer and Thewlis and Kracke were unable to verify the results obtained by Dennis that chronic and acute granulocytopenia can be produced when capsules containing broth cultures of pyogenic organisms are placed within the abdomen of rabbits. Meyer and Thewlis using 19 rabbits were unable to produce leukopenia or agranulocytosis by this method, with the exception that B. pyocyaneus caused acute leukopenia without a significant decrease in the percentage of neutrophils. Nor were Piersol and Steinfield able to produce long continued granulopenia in healthy rabbits by using the common bacteria.

This experimental work is interesting in view of the studies of C. W. Wells, who injected into rabbits huge doses of streptococci, staphylococci and typhoid bacilli and obtained an initial leukopenia followed by leukocytosis. Using pneumococci of high virulence, Long obtained similar results. In addition, Wells noted that when dead bacteria were injected into rabbits there followed a marked leukopenia in the peripheral blood and that during this peripheral leukopenia the blood obtained from the spleen and the hepatic parenchyma contained enormous numbers of leukocytes, a fact confirmed by Goldscheider and Jacobs. Thus, such bacteriologic data as relate to the etiology of agranulocytosis must be accepted with caution.

The symbiosis of several bacteria has been suggested as the etiologic agent, but proof is lacking.

In 1925 Schultz suggested the possibility that the toxic action of a filtrable virus has a special affinity for the myeloid tissue. As yet such a virus has not been demonstrated.

Typhoid.—In several cases of agranulocytosis that have followed typhoid prophylaxis (Kracke, Schur and Bromberg and Murphy) the condition has been thought to be due to an overwhelming foreign protein reaction in a sensitive person.

PATHOLOGIC ANATOMY

It is generally conceded that the essential pathologic feature of agranulocytosis is concerned with a severe degeneration of the granulocytic system associated with normal or nearly normal megakaryocytic and erythroblastic elements. Most frequently the bone marrow is hypoplastic or aplastic. The myeloblasts and myelocytes undergo pyknosis, nongranulation, vacuolation and hyalinization. These observations have been submitted by Koch, Petri, Uffenorde, Jackson, Zikowsky, Licht and Hartmann, Oppikoffer, Dameshek and others. Similar degenerative changes are observed in the myeloid elements in the less frequently reported cases in which the marrow is hyperplastic (Fitz-Hugh and Krumbhaar, Dameshek and Ingall, Baldridge and Needles, Buck, Fitz-Hugh and Comroe, Jaffé, Mettier and Olsan, David and Rose and Houser). Jaffé summarized these observations as follows:

> In both hyperplastic and the non-hyperplastic bone marrow the granulopoietic cells revealed severe degenerative changes. . . . I have obtained the impression that the specific granulation is the first to become affected while the nucleus remains intact for some time and may even divide by mitosis. The specific granules with all their outlines become indistinct and small vacuoles often appear around them. . . . The granules later dissolve into the vacuoles and pale purplish-pink droplets result which fuse together giving a vacuolated appearance to the cells. In the meantime the chromatin has become separated into coarse, sharply defined clumps and the nuclei have disappeared. An occasional mitosis may be detected in a cell which has been deprived of its granulation. The mitoses are, however, atypical, with short and clumsy chromosomes, and I think they do not pass beyond the metaphase. Finally, the nucleus shrinks, the cytoplasm coagulates, and the cell is dead. With the dissolution of the granules into the vacuoles the oxidase reaction becomes negative.

By virtue of these data it is assumed that some factor must be operative which either causes a cessation in the development of the white blood cells or prevents their migration into the blood stream. The cases of the hyperplastic type have been explained as due to a blockade which prevents the entrance into the blood stream of the mature leukocytes; and those of the aplastic type, by long continued blockade which leads to degeneration and destruction of the parent cells of the neutrophils.

Though anemia is frequently observed, especially in the prolonged cases, erythropoiesis proceeds normally; the lymphocytes, plasma cells and reticulohistiocytes of the bone marrow are normal, but, as Rose and

Houser, Hartwich, Van der Wielen and Jaffé have recorded, degenerative changes are often observed in the megakaryocytes, a fact that may explain the frequency of hemorrhagic diathesis. The giant cells are increased in number.

The ulcerations that occur in the oral cavity, tonsils, palatal region, larynx, stomach, anus, vagina and skin show extensive necrosis penetrating into the deeper tissues, with marked hemorrhages and numerous hyaline thrombi, associated with bacteria collected in huge numbers. Plasma cells are grouped along the border of the ulcer, in which is a diffuse lymphocytic infiltration but no neutrophils. The lungs often show confluent bronchopneumonia, with little evidence of inflammatory cellular reaction; subpleural hemorrhages are frequent; pleurisy with effusion is occasional. The pericardium displays many petechiae and ecchymoses, and the heart shows, like the liver and kidneys, parenchymatous degeneration. In the liver necrotic foci occur, and the Kupffer cells are swollen. The spleen is swollen and pulpy and rich in histiocytes and plasma cells. The kidneys show hyaline thrombi in the medulla and petechial hemorrhages. The lymph nodes show petechial hemorrhages. The reticulo-endothelial apparatus is proliferated not only in the bone marrow but also in the spleen, liver and lymph nodes. Rose and Houser and Rotter noted widespread necrosis and thrombosis of arterioles and venules.

MECHANISM

Severe reduction or absence of the neutrophils has been explained by three hypotheses: (*a*) destruction in the peripheral blood stream, (*b*) migration to various branches of the blood stream and to the viscera and (*c*) failure either of maturation of the myeloid elements in the bone marrow or of discharge of the mature granulocytes from the marrow into the peripheral blood stream. No convincing information has as yet been supplied to support the theory of destruction of the granulocytes in the peripheral blood stream. Though Brown found an increased amount of uric acid in the urine in his case, examination of the urine for this constituent has been generally neglected. No changes are observed in the white cell count or smear when the patient's blood is mixed with normal blood, and the injection of granulocytes from the patient's blood into animals produces no effect. The idea of an abnormal distribution of the neutrophils has little support. Studies of the numbers of the white blood cells and the neutrophils in capillary, venous and arterial blood in patients display no appreciable numerical differences. In addition, the significant feature in the pathologic picture of this disease is the unusual diminution or absence of the neutrophil in every organ and tissue.

Generally accepted, however, is the hypothesis that the disease process, whether bacteriologic, pharmacologic, endocrine, nutritional or of some other type, strikes as the primary and essential focus the myeloid elements of the bone marrow. The bone marrow is to be regarded, Doan has aptly suggested, as an organ subject to the same pathologic and physiologic changes as any other: hyperplasia and hypoplasia, sufficiency and insufficiency. What factors are responsible for these variations is only too little known. Lescher and Hubble supposed the existence of specific regulating factors for each of the cells of the bone marrow, and when one of these factors is deficient there results the disease characterized by this deficiency: agranulocytosis or thrombocytopenia or both, or even aplastic anemia when all are deficient. Beck expressed the belief that the essential pathologic change lies in the absence of a maturation factor for the neutrophils, and Fitz-Hugh and Krumbhaar said in this regard:

> It would seem probable that a maturation factor is at work either arresting development of white cells in their formative centers or producing degenerative changes in them before sufficient development for normal migration into the blood stream, or possibly a combination of both factors. This hypothetical factor would conceivably check the granular series of blood cells at the myeloblast-myelocyte stage in the bone marrow and the lymphocyte series at or near the lymphoblast stage in the spleen and the lymph nodes. Viewed from this standpoint the analogies to pernicious anemia are obvious. Pernicious anemia too has remissions and relapses. It, too, is as yet an idiopathic disorder with probably a constitutional background of prime importance. Its relapses are characterized by megaloblastic hyperplasia of the bone marrow caused by some maturation inhibiting factor, directed against the red cell series.

Doan suggested the possible importance of the lack of a chemotactic factor and pointed out that nucleic acid and its decomposition products stimulate the bone marrow to pour its myeloid elements into the peripheral blood stream. He observed that when administered to laboratory animals these substances caused myeloid hyperplasia in the bone marrow and a marked increase in the white blood cell count. He stated:

> Nucleic acid and its degradation products exert a chemotactic effect on normal foci with a prompt effective increase in the delivery of granular leucocytes to the peripheral circulation under a controlled physiologic or rhythmic mechanism. . . . A short course of injections stimulates a myeloid hyperplasia of normal marrow without otherwise injurious consequences, which is reflected by a relative and absolute increase in the amphophilic granulocytes in the blood stream of rabbits.

When the neutrophils break down, nucleic acid products are formed, and these stimulate the myeloid tissue; whatever the cause of neutropenia in agranulocytosis, these products are greatly diminished in the blood stream.

Besides maturation, regulation and chemotactic factors, what rôle do vasomotor and nervous activities play? And what are the factors concerned in the delivery of the granulocytes to the circulation? These are basic problems confronting the student of this disease.

What is the relationship between the fall in the number of neutrophils and the onset of the clinical symptoms? Data have accumulated which point convincingly to the conclusion that the myeloid tissue of the bone marrow becomes insufficient, whether owing to cryptogenic factors, toxins, bacteria or medicaments; the neutrophils of the peripheral blood are not replaced when they die, and soon the blood shows an alarming scarcity or absence of these elements, permitting the entrance into the blood of bacteria at vulnerable points, creating septicemia, which is fatal. Schultz, Friedemann, Meyer, Carter and Domarus reported cases in which angina was distinctly secondary, and Kommerell, Reye and Bock and Wiede noted the typical blood picture before the onset of the symptoms. These observations were confirmed by Hunter, Bantz, Ehrmann and Preuss; Rutledge, Hansen-Pruss and Thayer, and Lauter, Leon and Lindbloom. Rutledge, Hansen-Pruss and Thayer described a remarkable case of cyclic agranulocytosis beginning in a boy at the age of 2½ months and occurring every twenty-one days for twenty successive years. Preceding each attack the neutrophil and white blood cell count underwent a distinct fall. Jackson and Parker reported the case of a patient with a white blood cell count of 500 before the appearance of any clinical symptoms or signs, and on the fifth day there was a prompt rise in temperature, with chills, headache, prostration and sore throat. Roberts and Kracke had an unusual opportunity to follow in detail a single case illustrating the sequence of events. In a woman aged 72 with a normal blood picture there suddenly developed weakness, exhaustion, stupor, fever and rapid pulse. The white blood cell count was 2,050, and no polymorphonuclears were present. Though necrosis of the tongue developed, she recovered and became normal clinically and hematologically in two months. After that, however, a second attack developed in which the white blood cell count fell, and the neutrophils disappeared completely, but the patient was clinically well. It was only after four days of complete agranulocytosis that there developed symptoms of stupor, necrosis of the tongue and then pneumonia and finally death. Abrahams, however, described a case of pure agranulocytosis which persisted for fifteen days without the development of sepsis or any more serious manifestation than malaise.

CLINICAL COURSE

Whether of primary or secondary origin, the clinical course of agranulocytosis is always the same, just as the course of pernicious anemia is typical, whether caused by idiopathic factors or by syphilis

or Diphyllobothrium latum. The disease is characterized by an onset of premonitory symptoms, consisting of headache, malaise, weakness and anorexia, followed by ulceration and necrosis in the gastro-intestinal, respiratory or genito-urinary tract or of the skin. Most commonly this gangrenous process develops in the pharyngeal or oral cavity, with dysphagia and sore throat; in the upper part of the larynx, with dyspnea and swelling of the neck, and in the vagina or the anus or on the skin, with local symptoms. Angina is not always present, nor is ulceration. The course is usually stormy, with the temperature ranging between 102 and 105 F., with chills, sweats, delirium and early prostration. A hemorrhagic diathesis and icterus are common. The spleen may be slightly enlarged. Some degree of anemia commonly exists, with alarming neutropenia or complete absence of neutrophils and usually leukopenia. Septicemia follows, and in from 65 to 75 per cent of cases death ensues in from four to six days. Should the myeloid tissue respond, the stage of sepsis is prevented or overcome, and the patient may survive, not infrequently long enough to be precipitated into the throes of another attack; or, as happens less frequently, he may recover completely.[1]

Only one feature is essential for the diagnosis—severe neutropenia. But who will say how severe the neutropenia must be for the diagnosis to be established? Primary and secondary agranulocytosis may occur coincident with anemia, thrombopenia or both, and each of these may be slight, moderate or severe. It is often impossible to draw a sharply demarcating line when the hematologic picture merges into the realm of thrombopenia or aplastic anemia.

PRIMARY AGRANULOCYTOSIS

In this study the subject is divided for convenience into primary and secondary agranulocytosis. The primary type refers to that group of cases in which a specific causative agent has not been found. It is probable that future observation and investigation will show this group to be of secondary origin. The secondary type includes the group of cases in which the condition is caused by medicaments, chemicals or sepsis.

The theories that have been advanced to explain the nature of primary or idiopathic agranulocytosis fall into one of the following groups: infections or toxins, aplastic anemia or leukemic and developmental, vitamin, anaphylactic or endocrine factors.

Infection and Toxins.—The most popular of these conceptions is the first, supported by Roch and Mozer, Baltzer, Hunter, Weiss, Bock and

1. An increase in the number of monocytes in the peripheral blood is a favorable prognostic sign (Lichtenstein, Miloslavich and Murphy and Schilling), and a rapid sedimentation rate is an ill omen (Benhamou and Domarus).

Wiede, Versé, Leon, Fitz-Hugh and Comroe, Reye and Wohlwill, Petri, Lovett and many others, who have maintained that the essential process is one of sepsis, either specific or nonspecific, which overwhelms the bone marrow in a susceptible person of low resistance. Some have considered the disease to be analogous to noma of the ancients (Türk, Stursberg, Marchand, Schultz and Koch); others have believed that it is related to tropical phagedena (Plehn), and still others have believed that it is related to tuberculosis. Some have raised the question of the action of powerful toxins which either paralyze the bone marrow or produce a negative chemotactic effect on the granulocytes of the bone marrow. Occasionally carcinoma and lymphosarcoma produce marked depression of the bone marrow without demonstrable invasion of this organ, leading one to suspect toxins (Piersol and Steinfield). Jacobson offered the conception that the myelocytes, which, according to Sabin, are developed in the open sinusoids, are exposed to high concentrations of toxins carried in the blood that directly bathes these cells.

Aplastic Anemia.—In 1925 Frank declared that agranulocytosis is only a part of aleukia or panmyelophthisis or aplastic anemia. Zetterqvist saw truth in this idea, for in many cases, as previously noted, agranulocytosis is associated with anemia and thrombopenia. Duke offered the interesting suggestion that the disease is an atypical aplastic anemia acting selectively on the granulocytic centers, the result being an infection of such great severity that death occurs early without the opportunity for the anemia or thrombopenia of aplastic anemia to develop. In addition, gold, bismuth, arsphenamine and benzene have each produced depression of one, two or all three of the constituents of the bone marrow, indicating possibly a kinship between agranulocytosis, thrombopenia and aplastic anemia. Diguglielmo has entitled the syndrome acute partial aplastic myelosis.

Among those who have expressed the belief that agranulocytosis is a relative of the leukemias are Pelnář, Strumia, Leon, Hirschfeld, Mouzon, Roch and Mozer, Naegeli, Sternberg and Brogsitter and Kress. The literature records cases in which acute leukemia developed in a patient with an agranulocytic blood picture, but these probably best fall into the group of instances of aleukemic leukemia. Jaffé has stated that the disease may be a terminal complication of aplastic anemia, myelogenous and lymphoid leukemia and Hodgkin's disease.

Hypoplasia of Bone Marrow.—Many writers have adhered to the theory of hereditary hypoplasia of the bone marrow, an idea first suggested by Türk and later emphasized by Lauter, Ehrmann and Preuss and Feer. Roch and Mozer and Dahlgreen claimed that this abnormality becomes apparent during infection. But agranulocytosis is often seen developing in patients in whom the reaction to infection both

previous and subsequent to the attack of agranulocytosis is normal, and, furthermore, nucleic acid injected into such patients who have survived the disease produces a normal neutrophilic response (Lichtenstein).

X Factor.—Castle has obtained evidence that some disorder of the stomach plays a part in the etiology of pernicious anemia. Rosenthal has proffered the question as to whether such an unknown factor may be operative in agranulocytosis.

Vitamins, Foods and Minerals.—Though close scrutiny of the diets of patients with agranulocytosis fails to disclose any significant data, Miller and Rhoads have succeeded experimentally in producing neutropenia in dogs by feeding them the Goldberger black tongue-producing diet. Attention is also called to carbohydrate, fat, protein and mineral deficiency in foods.[2]

Anaphylaxis.—Nothing can be concluded from the present knowledge of anaphylaxis. Only suggestive data are supplied in the literature (Rutledge, Roberts and Kracke, Baldridge and Needles, Phillips, Baldridge, Hare and Childrey and Fondé). Kommerell has expressed the opinion that bacteria or their toxins sensitize the bone marrow, and the resulting shock is exhibited in a blockade or arrest of maturation in the bone marrow. Pepper asked:

> Is it possible that an allergic person experiences sharper drops in the leucocyte count physiologically than in the normal subjects and negligible causes bring about an allergic leucopenia? If at the onset of such a reaction a tooth is drawn or some other opportunity for bacterial invasion occurs the picture of Schultz's syndrome may be present. It is possible that in a person who is allergic to certain bacteria a slight sore throat is the starting point for an allergic leucopenia which then permits other bacterial invasions with a development of characteristic non-reacting local lesions.

Endocrine Factors.—Very early Friedemann suggested the importance of hormonal factors, as he had been influenced by the favorable effect of irradiation in agranulocytosis. Each of the organs of internal secretion has been incriminated since then, deficiencies of ovarian and pituitary secretion having been particularly mentioned. In 17 of his 18 cases of agranulocytosis occurring in young women, Thompson observed that subjective symptoms occurred within one or two days of the onset of the menstrual period. Six of these patients had one or more recurrences, and each recurrence coincided with the onset of catamenia. Rid-

2. John H. Stokes, of Philadelphia, and S. William Becker, of Chicago, have called attention to the frequency of neurodermatitis, a cutaneous eruption occurring in the highly nervous hypersensitive patient and developing under the pressure of physical or mental strain. If disease of the skin may ensue as a result of a neurogenic factor, is it improbable that agranulocytosis may be produced by a similar cause?

path found that 80 per cent of all cases reported have developed within the menstrual age and that the symptoms have appeared one or two days after the onset of catamenia. Jackson and Merrill reported a similar experience. The case of cyclic agranulocytosis reported by Rutledge, Hansen-Pruss and Thayer has shown the absence of female sex and gonadotropic hormones synchronously with the fall in the white blood cell and neutrophil counts.

Sigaard Andersen noted a rise in the granulocyte count after the administration of thyroid, and Lichtenstein, after thymus; some have advocated the use of spleen.

The cases of cyclic agranulocytosis, as reported by Rutledge, Etipol, Doan and others, suggest that the controlling influence may be similar to that of other cyclic conditions, such as hibernation, sleep, estrus and menstruation, which according to Cushing are controlled by the hormones liberated by the diencephalopituitary apparatus.

The administration of yellow bone marrow to patients suffering from agranulocytosis has given gratifying results in some cases. Employed in 1933 by Watkins and Giffin, it has been used by Flipse, of Miami, and others. Marberg, of the Otho S. Sprague Institute, Chicago, has perfected a concentrate of yellow bone marrow which has proved potent. Fenger stated that its greatest worth is appreciated in cases of acute agranulocytosis, in which after its use the neutrophil and white blood cell counts rise sharply.

Beck said:

> A maturation factor for erythrocytes has been found; it now remains to find a maturation factor for granulocytes. Chemical analysis of bacteria known to cause a sustained leucocytosis, owing to the fact that they supply both a chemotactic and a maturation factor, might lead to a solution. It seems more logical to search within the body for a specific organ extract regulating granulopoiesis. Animal experimentation with the removal of different glands of internal secretion or the destruction of other tissue by various substances with a careful check on the granulocytes might lead to valuable information not only as to etiology but also to treatment.

SECONDARY AGRANULOCYTOSIS

Though the most exacting history obtained from many patients suffering from this disease has revealed no responsible factor, it is felt by some that many of this primary group can be shown to have taken a medicament that is under suspicion.

Secondary agranulocytosis is identical with the primary form in its pathologic picture, symptoms, course, prognosis and terminus. Its characteristic feature is its remarkable rarity, leading to the conclusion that the myeloid tissue in a certain few persons possesses an idiosyncrasy to arsphenamine, bismuth, gold, benzene, di-nitrophenol, aminopyrine, barbital and amytal—substances to which attention is now invited. The

cases in which the condition develops in the course of sepsis also fall in this group.

Arsphenamine.—Although arsphenamine was introduced into therapeutic use by Paul Erhlich in 1910, from six to nine years elapsed before attention was focused on the postarsphenamine blood dyscrasias by Evans, Lerride and Labbé and Langlois. These complications are very rare. Loveman collected reports of 64 cases of aplastic anemia, purpura haemorrhagica and agranulocytosis from the literature. Cole and his co-workers observed 2 cases of purpura haemorrhagica among 12,212 patients who received 78,350 injections of various arsenicals over a period of ten years. Aubertin and Lévy found in the literature reports of 28 cases of agranulocytosis following antisyphilitic therapy: 13 patients were males and 15 females, the ages varying from 11 to 50 years, the average being between 20 and 40 years. Most of the subjects with this complication are robust and free from any pathologic complication. Postarsphenamine accidents are observed most frequently in women, according to Emile-Weil and Ishwall. The disease appears at ages ranging from infancy (hereditary syphilis) to nineteen years after the appearance of chancre. The type of arsphenamine does not seem to be important: arsphenamine, neoarsphenamine, sulfarsphenamine, silver arsphenamine or other preparations. The doses administered have never been greater than the average. The date of occurrence is variable, in many cases being during the first series of injections but in most instances during the second and third series. The time that elapses from the administration of the last injection to the development of the disease varies from one to eight days, with itching of the skin, headache, sore throat, vomiting, malaise and fever as the earliest symptoms. Many of the patients show early ulcerative necrotic anginal lesions and hemorrhagic manifestations. In some of the cases the picture conforms to Schultz' description; some patients have mild or marked anemia, and still others have anemia with thrombopenia—all grades are encountered merging with aplastic anemia. Dodd and Wilkinson stated that an initial stimulation of the blood-forming elements precedes a subsequent severe depression. The mortality is about 50 per cent. Autopsy reveals a complete or almost complete disappearance of the cells of the myelocytic series, identical to that noted in idiopathic agranulocytosis and benzene poisoning.

Arsphenamine contains the benzene ring, but there is no evidence that it breaks down into benzene in the body. According to Cushny, when arsphenamine is injected intramuscularly or subcutaneously, arsenic appears in the urine and stools, disappearing from the urine in from ten to fourten days and from the stools later. When injected intravenously it appears unchanged in the urine in from five to ten minutes and persists in this form for five or six hours; thereafter arsenites and

arsenates are found in the urine for several days and in the stools for a lesser period of time. When absent from the excretions, arsenic can no longer be found in the blood, though it may occur in the liver, bone marrow and kidney. Though from 50 to 65 per cent of the arsenic injected can be regained from the urine, nothing is known of the remaining 25 per cent or more.

The rarity of agranulocytosis due to arsphenamine, in view of the extensive use of this drug, suggests that in a certain few cases the bone marrow is idiosyncratic to this drug.

Bismuth.—Agranulocytosis following bismuth therapy has been reported by Silduff and McMann, Mouquin and Fleury, Sézary and Boucher, Aubertin, Blankstein and Lehmann. It is reported associated with anemia or thrombopenia or both and of mild or severe grade. It is of interest to note that a good deal of bismuth is used in cases of ulcers of the stomach, gastro-enteritis, ulcerative colitis and diarrhea, and yet agranulocytosis has not been reported in this group of cases. Certainly syphilis has not been demonstrated to exert any rôle in disposing a patient to this complication.

Mercury and Silver.—Some authors have suggested that mercury and silver are possible causes.

Gold.—Extensively used in the therapy of chronic rheumatism, pulmonary tuberculosis, lupus erythematosus, leprosy and sarcoid, gold salts are responsible not only for cutaneous, mucous, digestive, renal and hepatic lesions but also for thrombopenic purpura, aplastic anemia and agranulocytosis. Since 1919 there have been about 30 cases of these blood dyscrasias reported, of which 2 (in women) were instances of agranulocytosis. Ameuille and Braillon, Jacob and Douady, Achard, Coste and Cahen, Emile-Weil, Jacquelin and Allanic, Emile-Weil and Bousser, Ramondi and San Giovanni, Bonafé and Mollard, Farjon, Laignel-Lavastine, Reye, Fourcade and Jauneau, Stugl, and Nardi have contributed to this subject. About 80 per cent of these cases occurred in women and all in France, perhaps because of the popularity there of gold as a medicament. Each of the gold products sanocrysin (sodium gold sodium thiosulfate), aurocantan, triphal, lopion (sodium gold thiourea benzoate), solganol B (aurothioglucose), aurophos (the sodium gold double salt of an amino-arylphosphinic acid), colloidal gold and others have been responsible. The accidents occur at variable times during the course of injections, sometimes as early as the third or fourth injection. The symptoms are similar to those seen in "arsphenamine agranulocytosis"; especially marked is fever with minimal or maximal hemorrhagic manifestations involving the skin and viscera.

Benzene.—A close similarity exists between agranulocytosis and benzene poisoning, so much so as to suggest that the benzene ring

(contained in arsphenamine and in di-nitrophenol) is an etiologic agent. Orzechowski, Barker, Flandin, Aubertin, Poummer, Baldridge and Hansmann and Kracke have each produced pure agranulocytosis using benzene experimentally. They discovered that the smaller the doses of benzene employed, the more selective the affinity for myeloid tissue. The picture of the destruction of white blood cells as seen in the bone marrow in agranulocytosis is closely identical to that seen in benzene poisoning. The experiments of Selling, who injected benzene into rabbits, are enlightening. Not only are the parenchymal cells of the hematopoietic tissue destroyed but the white cells of the peripheral blood. The myeloid suffers more than the lymphoid tissue, and the polymorphonuclears of the peripheral blood are more greatly affected than the lymphocytes. Though the erythoblastic tissue is destroyed, the erythrocytes of the peripheral blood are little affected. If benzene is given in adequate amounts the myeloid and lymphoid tissues can be made completely aplastic within three or four days; regenerative changes then begin, and after from fifteen days to three weeks these organs are completely regenerated. As regeneration progresses the blood picture approaches normal. In the bone marrow the process of regeneration begins with the formation of small circumscribed cell groups and islands composed of large lymphocytes, granulocytes and erythroblasts. These islands increase in size and number and then fuse with each other, and the reticulum becomes filled with parenchymal elements. In the early stages the young cells predominate with myeloblasts and myelocytes, and in the later stages they become rare. The small lymphocytes and polyblasts are most resistant to benzene and are found after the other cells disappear.

The pathologic picture is characterized by petechial and ecchymotic hemorrhages throughout all the viscera; the spleen becomes atrophic with the destruction of the lymphocytic elements, and the parenchymatous organs and bone marrow become fatty. With profound anemia, leukopenia and thrombopenia the bleeding time becomes increased, the blood clot fails to retract and the hemoglobin content is reduced. There is a decided lack of response to infection, symptomatically and experimentally (Winternitz and Hirschfelder, Camp and Baumgartner, and Kline and Winternitz). The studies of Horwitz and Drinker, Simonds and Jones and Hektoen have shown that there is a marked reduction in the thrombin-producing capacity, fibrinogen, lysins, precipitins and opsonins in the blood.

In many respects thorium, radium and x-rays have an effect that is very similar to that of benzene.

Di-Nitrophenol.—Unlike benzene, arsphenamine, bismuth and gold, di-nitrophenol does not produce any blood dyscrasia other than agranulocytosis. In 1933 Tainter, Stockton and Cutting first called attention

to the use of this drug for the purpose of stimulating metabolism in the patient with hyperthyroidism and effecting loss of weight in the obese person. Its principal toxic effects are diaphoresis, hyperthermia, urticaria, angioneurotic edema, jaundice and nephritis; and tachycardia, a fall in blood pressure, acidosis and stupor also have been noted. It has produced agranulocytosis in the cases reported by Hoffman, Butt and Hickey; Silver; Davidson and Shapiro, and Bohn. Again, idiosyncrasy to this drug was blamed.

Aminopyrine.—After Kracke suggested in 1931 the possibility that aminopyrine or its derivates [3] are important in the etiology of agranulocytosis, numerous reports (Watkins, Madison and Squier; Deversy; Holten, Nielsen and Transbøl, Jorgensen; Costen; Barfred; Zinninger; Seemann; Andersen; Randall; Hoffman, Butt and Hickey; Laren; Rawls; Zinberg; Katzenstein and Wice; Benjamin and Biederman; Groen and Gelderman; Corelli; Fitz-Hugh; Knudson; Moltke; Johnson; Fisher; Sturgis; Plum and others) have appeared in which the

TABLE 4.—*Gathercoal Survey of Prescription Ingredients on the Basis of Ten Thousand Prescriptions* *

	Hallberg-Snow Survey of 1907	Charters Survey of 1927	U. S. Pharmacopoeia and National Formulary Survey of 1931–1932
Aminopyrine (U.S.P.)	2.8	36.3	135.8
Pyramidon	2.8	34.0	94.5

* Published by the American Pharmaceutical Association, 1933.

drug is accused. Patented in Germany in 1896, aminopyrine has been used for the past twenty-five years in America and very extensively during the past fifteen years. According to the Gathercoal Survey of Prescription Ingredients aminopyrine was prescribed by physicians almost sixteen times more frequently in 1926 than in 1907 and seventy times more frequently in 1931 and 1932 than in 1907. About 153 cases (Kracke and Parker) have been reported in which there was a history of its use. In only a very few of this number, however, had the condition been proved to be due to the pyrazolon drug. The importance of aminopyrine as a causative agent is illustrated by several facts. Experimentally, Madison and Squier produced agranulocytosis in a single rabbit given allonal (allylisopropyl barbituric acid with aminopyrine); Miller observed a decrease or almost complete absence of granulocytes in the bone marrow following its use; and Climenko has shown that after administration to the rabbit of aminopyrine, antipyrine,

3. According to Watkins the barbiturates and amytal have in rare instances been responsible for agranulocytosis. Neostibosan (an antimony compound) has also been blamed.

phenylhydrazine hydrochloride, catechol (pyrocatechin) and orthoquinone the normal leukocyte response to nucleic acid is not evoked. Clinically, Madison and Squier, Plum, Benjamin and Biederman, Sturgis and others have reported cases in which the patients recovered from "aminopyrine agranulocytosis" and when small doses of aminopyrine were again administered the Schultz syndrome presented itself, some of the patients showing cutaneous reactions to the drug. When these patients ceased taking the drug an attack failed to recur. That aminopyrine can produce allergic phenomena is shown by the swelling of the eyelids, cheeks and lips, the blotches on the forehead and the backs of the hands, the malaise (Unger), the scrotal urticaria, the genital edema (Crohn) and the exacerbation of fixed eruptions, for which it may be responsible. The patch, intracutaneous and scratch tests give positive results for aminopyrine in certain rare cases (Meredith). These observations show that some persons possess an idiosyncrasy to aminopyrine. Also, some authors have expressed the belief that the striking incidence of agranulocytosis since 1922, its predominance in physicians, physician's families, housewives, medical students, nurses, hospital orderlies, druggists and dentists and its occurrence at the time of catamenia are to be explained by the use of aminopyrine and allied drugs. By virtue of these data it has been urged that the use of aminopyrine should be restricted or that when the drug is employed there should be careful observation of the peripheral blood picture.

That aminopyrine is only an occasional etiologic factor is supported by abundant experimental and clinical evidence. The attempt to produce agranulocytosis in the laboratory animal by the administration of aminopyrine has, for the most part, been a complete failure. Schilling, Kracke, Fitz-Hugh and Comroe, Markson, Kunde and her associates and others have arrived at this conclusion. In an effort to investigate the effect of aminopyrine on the white blood cell and differential counts I undertook a study of 120 animals (guinea-pigs, rabbits and monkeys) over a period of eight months. Aminopyrine was given orally to one group in doses ranging from a fraction of a grain to 3 drachms (5.3 Gm.), daily, and blood cell and differential counts were taken daily. The symptoms were stupor, diarrhea and loss of weight. Many of the animals died of pneumonia, and some from aminopyrine poisoning, but at no time was agranulocytosis observed. This work was repeated with subcutaneous, intraperitoneal and intravenous injections, but no change in the blood picture occurred. With another group an attempt was made to sensitize some of the animals that were treated, and these were given a one month rest period, after which the medication was again given, still without effect. Incidentally, huge doses of the drug were injected into a pregnant guinea-pig for one and one-half months, but the new-born guinea-pig and the mother both had normal blood

pictures. The next problem contended with was: Do severe anemia, damage to the bone marrow, starvation, chronic infection and toxemia, or cachexia, constitute the soil on which agranulocytosis develops when aminopyrine is administered? The animals in the first group in this series were bled daily until the red blood cell count fell to between 1,500,000 and 2,000,000, and the red cells in the smear showed anisocytosis, poikilocytosis, and polychromasia. Despite this preparation the white blood cell count failed to fall as a result of prolonged administration of the drug. Into the animals in the second group small quantities of benzene in olive oil were injected subcutaneously until severe neutropenia and anemia were produced. In most of the animals the white blood cell count fell to below 1,500. To one half of the animals in this group aminopyrine was given orally, and these animals showed, peculiarly enough, a more rapid rise in the white blood cell and polymorphonuclear differential counts than did the animals which were not given the drug. After the animals in the third group were starved for five days the drug was administered but without avail. In the animals in the fourth group broth cultures of B. subtilis, Str. viridans and suipestifer were injected subcutaneously, and one month later, with the infection still persisting, they were given heavy doses of aminopyrine orally for three weeks. The white blood cell counts were elevated during the period of aminopyrine treatment, and the differential counts showed a predominance of polymorphonuclears. Thus, administration of aminopyrine to guinea-pigs, rabbits and monkeys, both with and without preliminary anemia or injury of the bone marrow, failed to produce any appreciable granulocytopenia.

Many clinicians see no cause for alarm. Schilling, Dennig and Zontscheff observed an aggregate group of 280 persons to whom aminopyrine was given daily for a period of a year, but no pernicious leukopenia was observed. Gordon has noted that the various psychopathic institutions in the country where this drug is used constantly do not report the disease; nor has Archibald Hoyne observed this complication in the several contagious disease hospitals of Chicago where aminopyrine has been employed since 1929 as a more or less specific preparation for the therapy of measles. Custer has added that at the Philadelphia General Hospital, having a yearly admission of about 30,000 patients, the approximate consumption of aminopyrine during 1934 was 120,000 tablets; no agranulocytosis was noted in the 1,926 autopsies performed during that year. Aminopyrine is extensively used and in prodigious quantities in the United States, yet the idiosyncrasy to it is exceedingly rare.

Some investigators have given aminopyrine to patients suffering from acute agranulocytosis and have observed no untoward results. Jackson gave the drug to 3 patients, 2 of whom recovered and 1 died. Limarzi

and Murphy administered a total of 370 grains (24 Gm.) of aminopyrine to a patient during her fourth attack of acute agranulocytosis, and she survived. Marcus, similarly, gave doses of 2.5 Gm. of aminopyrine to a subject and continued the administration for twenty-one days throughout the course of illness, with no ill effects. At the March 1935 meeting of the German Congress of Internal Medicine, Naegeli, Dennig, Veil, Kissling, Neergaard and Schittenhelm said that they saw no reason for discrediting the drug.

In the light of present evidence aminopyrine is to be respected, like arsphenamine and bismuth, as a useful medicament but also as one to which a rare patient may be sensitive.

SUMMARY

Agranulocytosis is a disease of multiple etiology. Its aspect is being altered daily, and the tests of persistent clinical observation and experimentation are essential to mold it into acceptable form. At present all that is known is that agranulocytosis is a relatively new disease, which is universally distributed but especially throughout the United States, Germany, Denmark, England, France and Italy; that it attacks chiefly women between the ages of 40 and 60; that its essential process is one of degeneration of the myeloid cells in the bone marrow, causing a failure to replace the dying neutrophils of the peripheral blood stream, resulting in complete absence of the neutrophils and inviting septicemia, which often proves fatal several days after the insult to the bone marrow; that the "primary" form may be a result of infection, may be related to aplastic anemia or leukemia, may be a developmental defect or may be caused by vitamin deficiency or anaphylactic or endocrine factors, and that the "secondary" form develops from sepsis or in the rare person whose bone marrow is idiosyncratic to arsphenamine, bismuth, gold, di-nitrophenol, aminopyrine, barbital and amytal medication. Greater intimacy with this disease will undoubtedly reveal fewer and fewer cases of idiopathic or primary origin.

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Notes and News

University News, Promotions, Resignations, Appointments, Deaths etc.—In Georgetown University, Washington, D. C., Vincent J. Dardinski, associate professor of pathology and parasitology, has been appointed professor of anatomy.

N. S. Conant has been appointed associate professor of bacteriology at Duke University.

Paul Kimmelstien has been appointed associate in pathology in the University of Pittsburgh.

In the College of Medical Evangelists, Loma Linda, Calif., Albert Brown has been appointed instructor in pathology.

John I. Fanz, professor of pathology, bacteriology and hygiene in Temple University, Philadelphia, died Aug. 26, 1935. He was 44 years old.

Konrad E. Birkhaug, from 1925 to 1932 associate professor of bacteriology at the School of Medicine and Dentistry of the University of Rochester and for the past three years a member of the Institut Pasteur at Paris, now occupies the chair of experimental medicine at Michelsen Institute for Scientific Investigations, Bergen, Norway.

Frederick Robert Zeit, professor of pathology in the medical school of Northwestern University, Chicago, has died at the age of 71 years.

Society News.—The Georgia Association of Pathologists was organized Oct. 29, 1935, with seventeen charter members. The headquarters of the association will be in Atlanta. The officers are Everett L. Bishop, president; R. R. Kracke, vice-president, and T. F. Sellers, secretary-treasurer. Meetings will be held monthly.

The Pacific Northwest Society of Pathologists has been organized with the following officers: F. R. Menne, president; O. H. Nickson, vice-president; T. D. Robertson, secretary-treasurer.

Wisconsin Law on Blood Tests.—This law follows the New York State law on blood tests and provides that in cases of disputed paternity the court may order "blood tests to determine whether or not the defendant can be excluded as being the father of the child." These tests may be made by "duly qualified physicians" and by "other duly qualified persons."

Grants in Aid.—The next meeting of the Committee on Grants-in-Aid of the National Research Council will be held in March 1936. Applications for grants must be on file with the secretary, Clarence J. West, 2101 Constitution Avenue, Washington, D. C., not later than February 15 next.

The next meeting of the Committee on Scientific Research of the American Medical Association for the consideration of applications for grants will be held early in February 1936. Applications should be addressed to the committee at 535 North Dearborn Street, Chicago.

Obituaries

CHARLES NORRIS
1867–1935

Charles Norris was born in Hoboken, N. J., on Dec. 4, 1867. He died in New York on Sept. 11, 1935. He attended Cutler's school in New York, obtained his collegiate degree from the Sheffield Scientific School of Yale University in 1888 and graduated from the College of Physicians and Surgeons, New York, in 1892. A two year internship at the Roosevelt Hospital followed. Here he came under the influence of Francis Delafield, one of the earlier American masters of pathology and an outstanding clinician of his time.

Following two years at Göttingen and Vienna, Dr. Norris entered the department of pathology of the College of Physicians and Surgeons of Columbia University. Here, under the direction of T. Mitchell Prudden, he carried out investigations in pathology, bacteriology and toxicology. In 1899 he became instructor in pathology at Cornell, but in 1902 he returned to the teaching staff of Columbia.

In 1904 Dr. Norris gave up his full time academic career to become director of laboratories at the Bellevue Hospital. Here his talent for the organization and direction of scientific work, which was to become valuable to his community and to forensic medicine at large in his future career, had an opportunity for development.

The consolidation of its constituent parts into the greater city of New York led to intolerable conditions in the coroner's office. To the faulty functioning inherent in this office everywhere were added abuses and graft because a number of elective coroners, parts of whose jurisdictions had entered into the metropolitan consolidation, held authority in the greater city. In 1915 the state legislature abolished the office of coroner in the city of New York and replaced the divided authority of a number of coroners by that of a single office of chief medical examiner. This change was to become effective on Jan. 1, 1918. In the interval, as the result of a comprehensive civil service examination conducted by a special committee of the outstanding pathologists of the city of New York, Dr. Norris was appointed the first chief medical examiner. This office he held until his death.

It was as chief medical examiner that Dr. Norris did his most important work, and outstanding work it was in a hitherto neglected field of medicine in the United States. The medical examiner system had been in use in Boston since 1877, but in New York the problem

was a much more difficult one because of the larger field to be covered by a single office and of the greater volume of work. To this task of organization Dr. Norris at once bent his unusual ability along this line. The task was an especially difficult one, not only because an entirely new type of governmental agency had to be developed but because many employees of the old coroner system, whose morals and morale had been contaminated by work under that system, had to be taken over. This factor impeded the work of the medical examiner for many years. How well the task of organization was accomplished becomes evident to any one who investigates the records, the record system and the work routine of the office.

To excellent previous training in pathology and its allied sciences and to ability in organization Dr. Norris added other attributes that were important for the success of the new venture. The large amount of actual physical work that he did in the performance of necropsies was possible only for one of his large frame and powerful physique. His tact and sense of humor, both attributes of value at times in a democracy, soon made it possible for him to convince the politicians that the office of chief medical examiner was not just another political office run by just another politician but an agency that tried to do important public work in a scientific manner. His imposing figure and his professional bearing made him an excellent expert witness, and his learning and experience, his unfailing good humor and the quizzical twinkle of his piercing eyes set under huge, shaggy brows put to rout the verbal pyrotechnics of bombastic cross-examining attorneys. The work of the chief medical examiner of the city of New York was soon accepted at its full value by police and prosecuting officials, courts, compensation boards and insurance companies.

Dr. Norris was a kindly man. Being a kindly man he could be deeply hurt by unjust criticism. And being a kindly man he was deeply appreciative of the good opinion of his colleagues. Early in 1935 the New York Academy of Medicine awarded him its gold medal for scientific achievement and outstanding public service. In reply to a note congratulating him on this honor, I received a letter, written in Dr. Norris' own characteristic angular chirography, brimming with enthusiasm and encouragement and sincere appreciation.

Dr. Norris had been assistant professor of pathology in the medical school of Cornell University and professor of pathologic anatomy in the medical department of Fordham University. In 1933 he was made professor of forensic medicine in New York University and Bellevue Hospital Medical College.

The place of Dr. Norris as chief medical examiner will be hard to fill. But his successor will find a firm foundation of work already

accomplished on which to build further. If and when the rest of the country replaces the antiquated coroner system by the more modern and scientific agency of the medical examiner, the medical examiner's office of the city of New York will become the most fitting monument to the ability and memory of Charles Norris.

OSCAR T. SCHULTZ.

Abstracts from Current Literature

Pathologic Anatomy

EFFECT OF PERITONEAL RESORPTION ON THE LIVER. E. G. LAIRD, Virchows Arch. f. path. Anat. **291**:440, 1933.

A variety of substances in solution were injected intraperitoneally into mice and rats, and their effects on the liver studied histologically, to test out the thesis that substances resorbed from the peritoneal cavity by the blood stream are carried directly to the liver. The chemicals used were potassium iodide, sodium iodide, iodoform, arsenic, yellow phosphorus, manganese chloride, and ortho and meta toluylendiamine. The dosages used were such as proved fatal in from twenty-four to forty-eight hours. At short intervals after injection the animals were killed and subjected to histologic examination. Within fifteen minutes to one hour after injection marked fatty change of the hepatic parenchyma was evident. This progressed to vacuolar degeneration of the hepatic cells. Intravenous injection of the same chemicals had a much less marked effect on the liver. Ligation of the portal vein preceding intraperitoneal injection prevented or delayed the toxic action on the liver. The greater part of the injected potassium iodide was excreted in from three to six hours and of iodoform in from twenty-four to forty-five hours. The chemicals appeared in the bile within a short period after injection. It is suggested that intraperitoneal administration may be a valuable therapeutic procedure when a rapid and direct action on the liver is desired.

O. T. SCHULTZ.

XANTHOMA OF THE HEART. K. WOLFF, Virchows Arch. f. path. Anat. **293**:472, 1934.

A man aged 62 years had had an acute rheumatic infection fifteen years before his death. Seven years before death signs of chronic cardiac embarrassment appeared. A month and a half previous to death the symptoms of acute endocarditis developed. Necropsy revealed a chronic stenosing aortic endocarditis, recent ulcerative endocarditis of the aortic and mitral valves with perforation into the right auricle, and carcinoma of the esophagus. Especial attention is directed to the presence of groups of foam cells filled with cholesterol in the fatty tissue at the hilus of the kidney, in a mesenteric lymph node and in the heart, in which the right ventricular wall was most markedly involved. In the heart the foam cells occurred in areas of fibrosis in which there was more recent cellular proliferation. Wolff asks whether the xanthomatous condition and the valvular disease were separate and distinct processes or whether and in what manner the two processes were related to each other. His analysis leads him to conclude that the endocarditis and the lipoid deposition were distinct processes, but that they had a sequential relation to each other. The acute valvular disease activated the older inflammatory areas in the myocardium. In the presence of hypercholesteremia, which was not established by antemortem chemical examination and which is tentatively ascribed to the esophageal carcinoma, cholesterol was deposited in the activated granulation tissue. He suggests that inflammation in the presence of disturbed cholesterol metabolism may be an essential factor in Hand's (Schüller-Christian) disease.

O. T. SCHULTZ.

A CASE OF CONGENITAL ENCEPHALITIS. H. BRANDT, Virchows Arch. f. path. Anat. **293**:487, 1934.

In 1866 Virchow applied the name "congenital encephalitis" to a condition in new-born infants and young children characterized by areas of fatty degeneration

and sclerosis in the brain. The cerebral condition may be associated with palsies, idiocy or Little's disease. The cerebral lesion has in general been ascribed to trauma sustained during birth. In the case reported by Brandt, that of an infant who lived two days, the presence in the brain of areas of necrosis that had progressed to calcification indicated that the factor causing the cerebral lesions had acted during intra-uterine life. This factor he suggests may have been a circulatory disturbance, possibly transient in its action.

O. T. SCHULTZ.

HYPERPLASIA OF BRUNNER'S GLANDS. F. FEYRTER, Virchows Arch. f. path. Anat. **293**:508, 1934.

As a result of the careful examination of the duodenums of 2,800 subjects Feyrter recognizes and describes three forms of benign hyperplasia of Brunner's glands: diffuse and nodose hyperplasia, circumscribed nodular hyperplasia with single or multiple nodules, and adenoma. The first two forms were observed in 0.85 per cent of the cases studied. Circumscribed benign adenoma is more rare and was observed in 0.12 per cent. There was a significant but not absolute correlation between chronic renal damage and hyperplasia of Brunner's glands. This is ascribed to reactive hyperplasia following injury to glandular epithelium by excreted toxic substances. Adenomas are not the result of tissue misplacement. Previous investigators had noted hyperplasia of Brunner's glands at the margin of duodenal ulcers; Wolff observed a similar process in the scars of healed ulcers.

O. T. SCHULTZ.

ASBESTOSIS BODIES. E. BEINTKER, Virchows Arch. f. path. Anat. **293**:527, 1934. P. J. BEGER, ibid., p. 530.

This is a rather hair-splitting and controversial reply and rebuttal called forth by a previous article of Beger. Beintker maintains that the silicic acid liberated from inspired asbestos particles evokes a connective tissue proliferation the localization of which is different from that of the usual form of silicosis. The asbestosis bodies are the result of a protective reaction; they are pathognomonic of asbestosis but have no bearing on the clinical manifestations of the process. Beger admits that the harmful action of asbestos is due to liberated silicic acid but insists that the process in asbestosis in itself is no different from that in other forms of silicosis. The asbestosis bodies increase the liberation of silicic acid and hence are an essential factor in the more severe clinical course and the greater degree of tissue reaction in asbestosis as compared with silicosis. When asbestosis bodies are not formed, asbestosis may run as benign a course as ordinary silicosis.

O. T. SCHULTZ.

PRIMARY TUBERCULOSIS OF THE ESOPHAGUS. J. INCZE, Virchows Arch. f. path. Anat. **293**:540, 1934.

Tuberculosis of the esophagus may occur as the result of implantation, and then it may be primary; of involvement by direct continuity from adjacent tuberculous foci, or of hematogenous or lymphatic transport. The condition described by Incze was noted in a 10 year old idiot who had swallowed a solution of lye twenty months before death. Recovery was followed by stricture of the esophagus. Death was preceded by symptoms of tuberculous meningitis. Necropsy revealed a stricture of the esophagus at the lower level of the larynx and another at the level of the tracheal bifurcation. Between these the esophagus was dilated and was the site of caseous tuberculosis. Epithelium was absent in the tuberculous region. There was generalized miliary tuberculosis with no foci older than the esophageal lesion. The case is one of primary implantation tuberculosis in an esophagus scarred by the action of a caustic.

O. T. SCHULTZ.

ATHEROSCLEROSIS OF THE AORTA AS OBSERVED IN ONE THOUSAND NECROPSIES OF PERSONS OVER TWENTY YEARS OF AGE. E. DORMANNS and E. EMMINGER, Virchows Arch. f. path. Anat. **293**:545, 1934.

In this investigation the factors taken into account were: age by decades, sex, the degree of atherosclerosis of the various portions of the aorta (ascending portion, arch, descending portion and abdominal portion) and the degree of arteriosclerotic involvement of the mouths and of the peripheral portions of the coronary arteries. These data were analyzed separately for tuberculosis, carcinoma and syphilis, all other conditions being grouped together as controls. The incidence and severity of atherosclerosis was relatively slight in the ascending portion of the aorta, increased in the arch, decreased again in the descending portion, and again became more marked in the abdominal portion. Except for syphilis, the curves are much alike for the diseases studied and for the controls. In syphilis, involvement was marked as to both incidence and severity in the three thoracic portions of the aorta; it was somewhat less marked in the abdominal portion but above the level for tuberculosis and carcinoma and the controls. Severe atherosclerosis of the abdominal portion of the aorta was more frequent in women than in men, and coronary arteriosclerosis was more frequent in men. These differences in the sexes became more evident with advancing years up to the age of 70. Severe atherosclerosis was less frequent in cancerous persons than in the controls, the percentages for the various decades being higher for women than for men. Coronary sclerosis was relatively less frequent in the syphilitic group than in the others. In tuberculous persons the incidence of abdominal atherosclerosis was relatively lower and that of coronary sclerosis relatively higher.

O. T. SCHULTZ.

A MESENTERIC CYST WITH THE STRUCTURE OF AN ESOPHAGUS. S. FLODERUS, Virchows Arch. f. path. Anat. **293**:608, 1934.

A mesenteric cyst removed from a girl aged 11 years had a length after fixation of 7 cm. and a diameter of 2.5 cm. Its lumen was lined in greater part by multilayered squamous epithelium like that of the esophagus. The epithelium rested on a thick muscularis. In places the lining was like intestinal mucosa, with single-layered columnar epithelium and crypts of Lieberkühn. Groups of mucous glands were embedded in the wall. Floderus postulates an origin from pluripotent tissue separated from the entoderm in early embryonic life.

O. T. SCHULTZ.

HISTOLOGY OF THE PANCREAS IN NUTRITIONAL DISTURBANCES OF NURSLINGS. ST. MAHRBURG, Virchows Arch. f. path. Anat. **293**:682, 1934.

Histologic examination of the pancreases of thirty nurslings dead of nutritional disturbances revealed no characteristic or specific changes. The interacinar tissue was edematous and relatively prominent as the result of passive congestion.

O. T. SCHULTZ.

GYNECOMASTIA AND CIRRHOSIS OF THE LIVER. M. BERGONZI, Virchows Arch. f. path. Anat. **293**:697, 1934.

Reserving the term "gynecomastia" for diffuse non-neoplastic hypertrophy of the male mamma, Bergonzi notes that this condition is most often associated with cirrhosis of the liver, pulmonary tuberculosis, syphilis and tumor of the testis. From the Italian literature he has tabulated 101 examples of such association; many of the reports are clinical. Of 453 cases of gynecomastia recorded in the world's literature 60 (13 per cent) showed the association with atrophic cirrhosis of the liver. The association was first fully discussed by Silvestrini in 1923; mammary hypertrophy in hepatic cirrhosis is known as Silvestrini's sign. Bergonzi has previously reported 2 cases and reviewed the subject in an Italian monograph. In the present article he reports the findings in an additional case and discusses

the pathogenesis of gynecomastia in cirrhosis. The patient was a man aged 54 years at the time of death. Symptoms of cirrhosis of the liver became evident two years before death. At about the same time loss of sexual power was noted; this progressed to complete impotence. The gross and microscopic observations may be summarized as follows: interlobular atrophic cirrhosis of the liver with hemosiderosis of the liver, spleen, pancreas, hypophysis, thyroid and testes; atrophy of the hypophysis with increased colloid content of the pars intermedia and basophilic infiltration of the posterior lobe; atrophy and tubular degeneration of the testes; slight hyperactivity of the thyroid; bilateral glandular mammary hypertrophy. The pathogenesis of gynecomastia in cirrhosis of the liver is ascribed by Bergonzi to endocrine dysfunction, especially of the testes and hypophysis. In support of this view of the endocrine feminizing effect of hepatic cirrhosis in the male he notes that the female type of pubic escutcheon is observed so frequently in cirrhosis as to be of diagnostic importance, and he himself has frequently noted atrophy and tubular degeneration of the testes in cirrhosis. That gynecomastia does not occur more often is probably due to an underlying constitutional factor which modifies the feminizing effect.

O. T. SCHULTZ.

HYDATID MOLES IN CATTLE. A. F. FOLGER, Acta path. et microbiol. Scandinav., supp. 1934, p. 104.

This disease in cattle is rare; only four cases have been reported previously. Folger discusses in detail five cases of his own, and concludes that in cattle so-called hydatid mole frequently develops as a hyperplasia of the connective tissue of the chorion with no involvement of the epithelial elements. The morphologic variations are summarized as follows: (1) a formation of villi with or without cysts; (2) polymorphous tissue-like nodules that develop possibly from certain intravascular proliferations; (3) a structure similar to the choriocarcinoma of human beings which apparently arises from hypertrophic villi in which cysts form. Folger calls attention to the associated occurrence in cattle of hydatid mole and teratoma.

Immunology

COMPLEMENT FIXATION AS RELATED TO RESISTANCE AND ALLERGY IN EXPERIMENTAL TUBERCULOSIS. A. B. BAKER, Am. Rev. Tuberc. **31**:54, 1935.

In experimental work with tuberculosis vaccinated rabbits can be differentiated from nonvaccinated ones by the complement-fixation test. The titer of the antibody in vaccinated animals does not measure the existing allergy but appears to parallel the resistance of the animals to experimental tuberculosis. Antibody which has been produced by vaccination and which cannot be detected by the complement-fixation test is not destroyed but has left the circulation; it can be exfoliated by various stimuli.

H. J. CORPER.

THE DECOMPOSITION OF TUBERCULOPROTEIN, STARCH AND GELATIN BY DRY GRINDING. C. H. BOISSEVAIN, Am. Rev. Tuberc. **31**:542, 1935.

Prolonged grinding of starch causes it to change first into erythrodextrin and then into achroodextrin. Prolonged grinding of gelatin changes it into a peptone-like compound that is very soluble in cold water and unable to form a gel even at icebox temperature. Defatted tubercle bacilli consist mainly of an insoluble compound of specific polysaccharide and tuberculoprotein. This compound can be broken up by prolonged grinding into water-soluble protein, peptone and polysaccharide. Treatment with 4 per cent sodium hydroxide solution or boiling with dilute acid has the same effect. Water-soluble protein is hydrolyzed into peptone in dilute solutions.

H. J. CORPER.

A Comparison of the Antigenic Properties of Defatted Tubercle Bacilli and Their Derived Proteins. C. H. Boissevain, Am. Rev. Tuberc. **31**: 547, 1935.

Water-soluble proteins obtained from ground tubercle bacilli, from hydrolyzed bacilli and from filtered culture medium have the same tuberculin activity. Doses of from 1 to 40 mg. of defatted tubercle bacilli make guinea-pigs hypersensitive to 0.1 cc. of a 0.01 per cent solution of tuberculoprotein. The same doses of the insoluble residue obtained by grinding make guinea-pigs hypersensitive to 0.1 cc. of a 1 per cent solution. It was not possible to make guinea-pigs hypersensitive to a 1 per cent solution of tuberculoprotein by the injection of from 10 to 100 mg. of any water-soluble or alkali-soluble protein or peptone derived from the tubercle bacillus.

H. J. Corper.

Tetanus Toxin Not Transported in Peripheral Nerves. J. J. Abel et al., Bull. Johns Hopkins Hosp. **56**:84, 1935.

We have presented many considerations and many facts in support of our belief that tetanus toxin and dyestuffs injected in an aqueous medium intraneurally, subcutaneously, intramuscularly or intravenously are not carried in the axis-cylinders, the lymphatic vessels or the tissue spaces of peripheral motor nerves to the reacting cells of the central nervous system. We have also cited the recent investigations of anatomists who have traced the outflow of lymph from nerve trunks and have shown that it, like the lymph of other structures of the body, is added finally to the venous blood and not to the cerebrospinal fluid. We furthermore called attention to a series of investigations that were carried out by Abel and Abel and Turner in the years 1910 to 1914 in which it was conclusively shown that alkaloids and dyestuffs cannot be distributed throughout the body by any peripheral mechanism such as the "tissue spaces."

From the Authors' Summary.

Intradermal Antiserum Tests. L. Foshay, J. Allergy **6**:360, 1935.

Intradermal tests with certain antiserums, e. g., antitularense, antibrucella, etc., may cause the typical reaction of sensitization in the allergic sense as well as—and this is a new observation—simple erythema with central edema and complete absence of urticaria in patients with the corresponding infection. The reaction is specific and unrelated to sensitization with the serum. The erythematous-edematous reaction may be useful as a diagnostic aid. Approximately 0.04 cc. of a 1:10 dilution of the antiserum should be injected intradermally. The reaction usually appears within a few minutes.

The Occurrence of Antifibrinolytic Properties in the Blood of Patients with Acute Hemolytic Streptococcus Infections. W. S. Tillet, J. Clin. Investigation **14**:276, 1935.

A specific antisubstance directed against the fibrin-dissolving action of hemolytic streptococci was demonstrated in the blood of approximately 75 per cent of patients who recovered from acute streptococcic infections. The fibrin clot from the blood of patients who died of the infection was in no instance capable of inhibiting the bacterial fibrinolytic action. The antifibrinolytic response was demonstrable at the approximate time of recovery in some patients, and in others it was not detected until the second to fourth week of convalescence. Although there were exceptions, the specific response appeared during the course of erysipelas earlier than it did during that of any acute streptococcic infection of the upper respiratory tract. Antifibrinolytic resistance developed in twenty-eight patients. All of them recovered, and their convalescence was not interrupted by a reactivation of the streptococcic infection. Seventeen patients failed to acquire humoral antifibrinolytic properties. In seven of those included in this group the disease was self-limiting and convalescence uneventful. Of the remaining ten,

seven died and three had prolonged illnesses due to exacerbations of active streptococcic infection. In a few cases of active rheumatic fever and acute nephritis which were studied antifibrinolytic resistance was usually present. The response did not differ in its development from that which occurred in cases of acute streptococcic infection without the visceral involvements of rheumatic fever or acute nephritis.

FROM THE AUTHOR'S SUMMARY.

ANAPHYLAXIS WITH POLLEN. C. BERNSTEIN JR., J. Exper. Med. **61**:149, 1935.

Guinea-pigs given intracutaneous and subcutaneous injections of relatively small amounts of an extract of the pollen of burweed marsh-elder did not show anaphylactic response to intravenous shock doses of this material three weeks later. Animals sensitized with horse serum before or at the time of the injection of pollen extract could be shocked after an interval of three weeks with pollen extract alone. The possible rôle of this underlying sensitivity is discussed.

FROM THE AUTHOR'S SUMMARY.

HYPERSENSITIVENESS IN DOGS AFTER EXPERIMENTAL PNEUMOCOCCUS LOBAR PNEUMONIA. L. T. COGGESHALL, J. Exper. Med. **61**:235, 1935.

The data derived from the investigations indicate that dogs do not acquire hypersensitivity to Pneumococcus as the result of experimental lobar pneumonia. This inference is based on the following findings: Fifteen dogs were given type I and type II pneumococcic lobar pneumonia and following recovery were tested for hypersensitiveness by means of intrabronchial and intracutaneous injections of the autolysate of the homologous type of Pneumococcus. Seven dogs had a pulmonary lesion discernible in the x-ray film at the site of the intrabronchial injection of the autolysate; three of these dogs were normal controls. No evidence of a positive skin reaction was found in any of the fifteen dogs, many of which received repeated infections and intradermal injections of the autolysate. Subsequent infections in the same animals were definitely milder than the initial infection. The infections following the intrapulmonary and cutaneous administration of the autolysate were practically of the same intensity as the initial infection. The temperatures, pulse rates, white blood counts and differential blood pictures showed no significant variations following intrapulmonary injection of the autolysate. Tests for the acquisition of humoral immune bodies following the injection of the autolysate and recovery from the experimental disease showed the presence of these substances in some dogs and their absence in others. Histologic study of the pulmonary lesions produced by the autolysate failed to reveal changes characteristic of an allergic reaction. However, the perivascular accumulations of large mononuclear cells observed in the lesions of the dogs which recovered suggest a locally accelerated reactivity of the fixed tissue cells to the products of Pneumococcus.

FROM THE AUTHOR'S SUMMARY.

THE SEROLOGICAL DIFFERENTIATION OF HEMOLYTIC STREPTOCOCCI FROM PARTURIENT WOMEN. R. C. LANCEFIELD and R. HARE, J. Exper. Med. **61**:335, 1935.

The majority of the strains of hemolytic streptococci from puerperal uterine infections were identified serologically as members of the group A described by Lancefield. The majority of the strains isolated from the birth canals of women in whom the puerperium was afebrile were not members of group A. Two new serologic groups of hemolytic streptococci, F and G, are described.

FROM THE AUTHORS' CONCLUSION.

LOCAL SKIN REACTIVITY TO BACILLUS TUBERCULOSIS. G. SHWARTZMAN, J. Exper. Med. **61**:369, 1935.

New toxic substances in certain tuberculin, old tuberculin and filtrates of Bacillus typhosus are described. These substances are capable of eliciting the

hemorrhagic necrosis characteristic of local skin reactivity provided heterologous bacterial filtrates of high potency are used for either the intradermal or the intravenous injection. The toxic substances apparently have no relationship to the tuberculin substances proper. The experiments with inactive preparations also demonstrate in rabbits a state of hypersensitiveness to tuberculin, old tuberculin and bacteria-free culture filtrates in the absence of tuberculous foci. The reactions are elicited provided the tissues are rendered vulnerable through contact with certain soluble bacterial factors capable of eliciting local skin reactivity to bacterial filtrates and provided the tuberculin or the tubercle bacillus culture filtrate is injected intravenously into immunized rabbits.

FROM THE AUTHOR'S SUMMARY.

GRADING OF LOCAL SKIN REACTIVITY TO BACTERIAL FILTRATES. G. SHWARTZMAN, J. Exper. Med. **61**:383, 1935.

In this paper are described methods for grading local skin reactivity to bacterial filtrates. The grading is accomplished by titration of the skin-preparatory factors and by studies of the duration of the ensuing reactivity. It was found that the duration of reactivity depends on the mode of preparation of the filtrates and on the micro-organisms employed. Thus, it lasts for ninety-six hours with Meningococcus "agar washings" filtrates and for seventy-two hours with Bacillus typhosus "agar washings" filtrates; it disappears within forty-eight hours with B. typhosus tryptic digest broth culture filtrate and B. typhosus "agar washings" filtrates previously heated in the Arnold sterilizer for twenty minutes. Comparative titrations of the preparation employed demonstrate that the duration of reactivity is in direct relationship to the reacting potency. It is also shown that the skin-preparatory potency of the filtrates and the duration of the ensuing local reactivity are not modified by cellular anaphylactic sensitization (Arthus' phenomenon) to animal proteins. The exposure of tissues to the effect of certain soluble bacterial factors induces a high susceptibility to humoral toxic principles resulting from intravascular antigen-antibody interaction.

FROM THE AUTHOR'S SUMMARY.

THE NEUTRALIZATION TEST IN POLIOMYELITIS. J. R. PAUL and J. D. TRASK, J. Exper. Med. **61**:447, 1935.

The difference between two human and two passage strains of the virus of poliomyelitis when tested by this method amounted to about 25 per cent, and there was less power in normal adult serums to neutralize human than passage strains of virus. The difference between the two human strains amounted to 15 per cent, and that between the two passage strains to 8 per cent, the last figure falling within the limits of the experimental error of the method. The extent to which these findings affect certain concepts with regard to the epidemiology of poliomyelitis based on neutralization experiments with passage strains cannot be determined from the data presented in this paper, except that they more or less confirm the view previously derived from such experiments that from 70 to 95 per cent of normal urban adults possess in their blood a substance which neutralizes the virus in a given amount. However, certain other indications appear when the present results are supplemented by those previously obtained (Paul and Trask: *J. Exper. Med.* **56**:319, 1932; **59**:513, 1933). Primarily, the authors have found no relation between the clinical acquisition of poliomyelitis and the presence of a substance in the serum which neutralizes a passage strain of the virus. With a passage strain the results seem rather to bear a closer relationship to age than to illness. With a human strain results have been obtained in which there is some evidence, shown only in the juvenile group, that acquisition of the clinical disease is accompanied by the appearance of antiviral properties in the blood.

FROM THE AUTHORS' SUMMARY.

THE PRECIPITIN REACTION BETWEEN TYPE III PNEUMOCOCCUS POLYSACCHARIDE AND THE HOMOLOGOUS ANTIBODY. M. HEIDELBERGER and F. E. KENDALL, J. Exper. Med. **61**:559 and 563, 1935.

The precipitin reaction between the specific polysaccharide of Pneumococcus type III and the homologous antibody formed in the horse can be accounted for quantitatively by assuming the chemical combination of the components in a bimolecular reaction, followed by a series of competing bimolecular reactions which depend on the relative proportions of the components. These reactions lead to the formation of larger and larger aggregates until precipitation ultimately occurs. The mathematical formulation of this theory on the basis of the law of mass action (Guldberg and Waage) is described. The derived expressions are shown to be in accord with the experimental findings, and the constants used in these expressions are shown to have definite significance. In spite of the wide variation in the properties of individual serums these expressions permit complete description of the behavior of an unknown serum with S III without an unduly burdensome number of analyses. The quantitative theory presented has been found applicable to other instances of the precipitin reaction, as will be shown in subsequent papers. FROM THE AUTHORS' SUMMARY.

LOCAL DISPERSION OF INFECTIOUS AGENTS AS A FACTOR IN RESISTANCE. F. DURAN-REYNALS, J. Exper. Med. **61**:617, 1935.

Progressively decreasing quantities of bacteria of some twenty strains were utilized in experiments to determine the effect of dispensing the organisms in the rabbit's skin through the agency of an extract of testicle or an invasive staphylococcus. The same experiment was made with six strains of filtrable viruses. When the organisms introduced were above a certain number or quantity (the minimal effective concentration) the bacterial lesions were enhanced by spreading; on the other hand, when the number was less than this the lesions were partially or totally suppressed. The virulence and the minimal effective concentration were observed to be in inverse relationship. The lesions due to the filtrable viruses were enhanced by spreading even when the quantity of virus approached the minimal infective dose. This happened whether the virus caused severe or slight lesions. When Pneumococcus of the highly virulent type I was injected with the spreading factor into normal rabbits it yielded enhanced lesions even at practically the minimal infective dose; but when the resistance of the animal was raised with specific antiserum the lesions were totally suppressed owing to the dispersion of the bacteria. When such an experiment was repeated with a filtrable virus, that of vaccinia, no suppression took place as a result of the dispersion of the infective agent. FROM THE AUTHOR'S SUMMARY.

THE FIXATION AND PROTECTION OF VIRUSES BY THE CELLS OF SUSCEPTIBLE ANIMALS. P. ROUS, P. D. MCMASTER and S. S. HUDACK, J. Exper. Med. **61**: 657, 1935.

Methods were developed for a study of the relations existing between viruses and living cells. It was found that the virus of vaccinia and the virus causing the infectious fibroma of rabbits (Shope) rapidly become fixed on tissue cells freed as individuals and submitted to the viruses in suspension. This happens whether the cells are alive or have been killed with heat or ultraviolet rays. The virus does not come away during agitation of the cells with Tyrode solution and repeated washings with large amounts of it. The exposure of cells carrying virus to neutralizing antiserum fails to affect the virus significantly if the cells are alive, whereas if they are dead the activity of the virus is nullified. Cells freed as individuals from tissue cultures of the virus of vaccinia and the Shope tumor carry these viruses in abundance through repeated washings and if living protect them from the influence of neutralizing serum, whereas killed cells exert no such protection. The findings appear to throw light on the way in which viruses gain a

foothold in the host, and they suggest reasons for the persistence of some viruses in animals that have recovered and for the unsatisfactory results of serum therapy instituted during the course of virus diseases. The virus causing the Shope fibroma has been successfully maintained in cultures of the growth. It is closely associated with the cells, almost none being present in the culture fluid. Certain of its other attributes have been determined. The virus of vaccinia greatly damages the cells of cultures of rabbit embryo in which it is under propagation.

FROM THE AUTHORS' SUMMARY.

THE TYPE I MENINGOCOCCUS SPECIFIC SUBSTANCE. H. W. SCHERP and G. RAKE, J. Exper. Med. **61**:753, 1935.

This substance has been isolated and purified. It appears to be a sodium salt of a polysaccharide acid.

FROM THE AUTHORS' SUMMARY.

THE FORMATION OF AGGLUTININS WITHIN LYMPH NODES. P. D. MCMASTER and S. S. HUDACK, J. Exper. Med. **61**:783, 1935.

Agglutinins are formed within the draining lymph nodes of mice following intradermal injections of killed cultures of micro-organisms.

FROM THE AUTHORS' SUMMARY.

CONCENTRATION OF ANTIBODY IN IMMUNE SERUM. JOHN H. HANKS, J. Immunol. **28**:95, 1935.

A gelatinized solution of antigen furnishes a practical means of determining the antibody content of both weak and strong antiserums. The titer of as little as 0.03 cc. of serum can be determined by allowing an optimal amount of antigen to diffuse into increasing dilutions of the antiserums and reading the dilution in the last tube in which a ring is visible on the upper layer of the gelatinized antigen.

ELIZABETH MCBROOM.

THE MECHANISM OF THE TUBERCULIN REACTION. J. H. HANKS, J. Immunol. **28**: 105, 1935.

If a foreign protein (egg-white, horse serum) is injected into a tuberculous lesion of a guinea-pig or into an apparently normal testicle adjacent to an infected testicle there develops a specific cutaneous hypersensitiveness like that characteristic of the tuberculin reaction. A possible approach to the mechanism of the tuberculin reaction is suggested by this variation in the type of response to a foreign protein of an animal receiving an injection of the protein at the site of a tuberculous lesion.

ELIZABETH MCBROOM.

HYPERSENSITIVENESS AND IMMUNITY TO FOREIGN PROTEINS. F. H. Teale, J. Immunol. **28**:161, 1935.

Hypersensitiveness is due to that state of the tissues in which they cannot deal with specific antigen even when it is completely saturated with the homologous antibody. In immunity the tissues are increasingly capable of dealing with the antigen as the degree of immunity increases; the circulating antibody is of little moment. The greater amount of circulating antibody is not the main difference in the states of increasing immunity to the protein in question. In order to produce passive hypersensitiveness definite amounts of antibody are necessary; the amounts vary with the antigen against which the antibody is specific, again showing that the titer of the antibody in vitro is no exact measure of its effectiveness in the body. There is no special antibody causing hypersensitiveness; the antibody seems to be related to the ordinary lytic or precipitating one. These results again

show the preeminence of the state of the tissues in regard to immunity, of their capability of dealing effectively with the antigen, and the negligible part played by the circulating antibody as such. FROM THE AUTHOR'S CONCLUSIONS.

THE PHOTODYNAMIC EFFECT OF METHYLENE BLUE ON TETANUS TOXIN. K. M. LIPPERT, J. Immunol. **28**:193, 1935.

The toxic properties in a filtered broth culture of Clostridium tetani are rapidly diminished by the photodynamic action of methylthionine chloride (methylene blue) in certain concentrations. The inactivation of the tetanus toxin in the presence of dilute solutions of methylthionine chloride is more marked after exposure of the mixture to light for one hour than after shorter intervals of time. The antigenic property could not be demonstrated in tetanus toxin after partial destruction of its toxicity by exposure to light in the presence of dilute solutions of methylthionine chloride. An optimum concentration of this drug for the inactivation of the toxin by light is demonstrated. In the concentration used it does not inhibit the effect of the toxin in vivo. FROM THE AUTHOR'S SUMMARY.

A QUANTITATIVE STUDY OF SERUM PRECIPITIN IN ANAPHYLAXIS IN THE RABBIT. C. JACKSON, J. Immunol. **28**:225, 1935.

A high titer of precipitin for ovalbumin is not a guarantee that an animal can be fatally shocked by an injection of ovalbumin. The amount of ovalbumin necessary to produce shock does not bear a constant relationship to the titer of the precipitin. The highest percentage of deaths from shock occurred among female rabbits, the majority of these being pregnant at the time of the experiment.

ELIZABETH MCBROOM.

ARE ANTIBODY ACTIONS DUE TO SEPARATE ANTIBODIES? F. H. TEALE, J. Immunol. **28**:241, 1935.

Different manifestations of antibody activity are not due to the activity of the same immune substance acting differently under different physical conditions, etc., but are due to the activity of different antibodies. This can be shown by the difference in their development, by the observation that in some cases the agglutinin can be adsorbed, leaving the protective power of the antiserum intact, and by the fact that heat at 65 C. destroys the protective power and leaves the agglutinin uninjured. Attention has also been drawn to the fact that a serum may have a high titer of agglutinin and yet have no protective power and vice versa.

THE RÔLE OF PRECIPITIN IN THE REMOVAL OF INTRAVENOUSLY INJECTED ANTIGEN. J. T. CULBERTSON, J. Immunol. **28**:279, 1935.

Rabbits immunized against horse serum can dispose of horse serum injected intravenously more readily than can normal rabbits. Immune rabbits with circulating precipitin are somewhat better able to dispose of horse serum injected intravenously than are immune rabbits which have been permitted to rest until circulating precipitin has disappeared. Crystallized egg albumin injected intravenously in small amounts into specifically immunized rabbits cannot be detected in the circulation after its injection. The precipitin content of the serum of these animals is diminished following the injection of the antigen into the blood stream. It appears likely that the antibody both in the circulation and in the fixed tissues unites with the antigen introduced into the circulation. The quantity of antibody immediately available for such union is evidently much less in the fixed tissues than in the blood, the amount in the tissues being usually not over 25 to 50 per cent of that in the blood. When an amount of antigen significantly greater (by from 25 to 50 per cent) than that calculated to neutralize the circulating antibody is introduced all of the immediately available antibody is removed from the circulation

and from the fixed tissues and antigen can be detected in the blood. The amount of circulating precipitin against crystallized egg albumin is not significantly altered by the injection of numerous nonspecific substances into the circulation.

FROM THE AUTHOR'S CONCLUSIONS.

AN IMMUNOLOGICAL STUDY OF THE EFFECTS OF INTENSE SOUND VIBRATIONS ON EGG ALBUMIN. E. W. FLOSDORF and L. A. CHAMBERS, J. Immunol. **28**:297, 1935.

The coagulum produced by sonic irradiation of a solution of egg albumin has a much decreased antigenic activity and an altered specificity. The altered specificity of the coagulum is similar to the specificity of albumin denatured in other ways. The soluble fraction remaining after sonic irradiation is unaltered immunologically. Prolonged irradiation increases the amount of coagulum produced and then redisperses it into an opalescent sol of the same altered serologic specificity. Very prolonged irradiation decreases the amounts of both serologically native and altered proteins. Excellent agreement with respect both to antigenic activity and specificity was observed in the results with the Arthus phenomenon, the intradermal tests and the precipitin reactions. In some cases the intradermal test was somewhat more delicate than the precipitin reaction.

FROM THE AUTHORS' SUMMARY.

THE FLARING UP OF INJECTION SITES IN ALLERGIC GUINEA PIGS. L. DIENES and F. A. SIMON, J. Immunol. **28**:321, 1935.

In a guinea-pig that has been given an intracutaneous injection of human serum or turtle egg a flare-up at the site of injection can often be observed after a few days. This occurs at the time when skin sensitiveness begins to develop, usually on the fourth to sixth days. Both the flare at the original site and the skin test at this time are purely of the delayed type, and anaphylactic shock cannot be produced in the guinea-pig. In the reacting flare about the original site of inoculation the tissues show infiltration with mononuclear cells, which is characteristic also of the delayed type of skin reaction. It is pointed out that the developing allergy probably plays a rôle in the development of specific tissue reactions in the lesions of certain infectious diseases.

FROM THE AUTHORS' SUMMARY.

THE INDIVIDUAL AS A FACTOR IN ANTIDIPHTHERIA IMMUNITY. J. M. NEILL, J. Y. SUGG and L. V. RICHARDSON, J. Immunol. **28**:363 and 385, 1935.

The investigation is essentially an analysis of the antitoxin titers of the serums of a large number of guinea-pigs immunized by different methods and bled at six month intervals between the first and the third year following the last injection. The data indicate that the individual animal is a more important factor than the method of immunization in determining the titer of antitoxin at times remote from the last injection. Examples are given of the wide differences in individual guinea-pigs in respect to their loss of antitoxin. Some of the animals had such a marked capacity to maintain their immunity that their titers appeared approximately "level" over long periods; the time at which this "level" was reached and the height at which it was maintained appeared to be as much a characteristic of the individual guinea-pig as of the method of immunization.

FROM THE AUTHORS' SUMMARY.

THE SPONTANEOUS OCCURRENCE OF BRUCELLA AGGLUTININS IN DOGS. W. H. FELDMAN, F. C. MANN and C. OLSON JR., J. Infect. Dis. **56**:55, 1935.

By agglutination tests agglutinins of Brucella were found to be present in the serum of 52, or 10.4 per cent, of 500 dogs obtained as adults from rural environments. Serums from 15 of the reactors failed to give agglutination of the antigens

in dilutions greater than 1:12, whereas serums of 33, or 6.6 per cent, gave positive reactions in dilutions of 1:25 or greater. Serums of only 5 of the animals showed agglutination in dilutions of 1:100 or greater. Attempts were made to isolate Brucella abortus by inoculation of guinea-pigs with emulsions of tissues from 14 of the reacting animals; the results were negative. Dissemination of the infection from dogs with agglutinins against Brucella by cohabitation with normal dogs failed. None of the dogs with agglutinins against Brucella exhibited symptoms indicative of specific infection, and in none whose bodies were examined at necropsy was there pathologic evidence of disease due to Br. abortus. A study was made of the possible cross-agglutinability of Br. abortus and Bacillus bronchisepticus. Dogs and rabbits were utilized. Cross-agglutination of significant degree did not occur.

FROM THE AUTHORS' SUMMARY.

ANTIGENIC CHARACTERISTICS IN MAN OF CERTAIN PRODUCTS OF THE PNEUMOCOCCUS. L. D. FELTON, W. D. SUTLIFF and B. F. STEELE, J. Infect. Dis. **56**:101, 1935.

Certain fractions of the pneumococcus, treated under various conditions, produce in the human being a protective antibody response comparable in degree to that obtained with vaccine. However, the response to the various antigenic fractions differs from that to type I and type II vaccines to this extent: While the response to type I vaccine is largely homologous and that to type II vaccine only moderately heterologous, the response to the various fractions, though in different degrees, is much more heterologous.

Tumors

THE SCHUBERT-DANNMEYER TEST FOR CANCER. E. R. HOLIDAY and F. C. SMITH, Am. J. Cancer **23**:339, 1935.

A study of the diagnostic test for cancer devised by Dannmeyer, Schubert and Treplin is described. Forty-seven cases of cancer and forty-six control cases have been investigated. Dannmeyer's claim to a diagnostic accuracy of 95 per cent cannot be confirmed, though a certain degree of specificity seems indicated. The test in its present form is insufficiently reliable and too complicated for regular clinical use.

FROM THE AUTHORS' SUMMARY.

THE ACTION OF 1:2:5:6-DIBENZANTHRACENE ON OBELIA GENICULATA. S. P. REIMANN and F. S. HAMMETT, Am. J. Cancer **23**:343, 1935.

Observations made on the development of Obelia geniculata in cultures in sea water containing 1:2:5:6-dibenzanthracene to approximate saturation, and in control cultures in plain sea water and in sea water plus an equivalent amount of solvent for the test compound, show that the substance increases the proliferation of this organism.

FROM THE AUTHORS' SUMMARY.

RETROPERITONEAL XANTHOGRANULOMA. C. OBERLING, Am. J. Cancer **23**:477, 1935.

Xanthogranuloma consists of inflammatory tissue infiltrated more or less extensively by foam cells containing cholesterol ester, cholesterol and neutral fats. The abundant proliferation of histiocytic or fibrocytic elements in some areas suggests a true tumor process, but xanthogranuloma is to be distinguished from xanthoma and xanthosarcoma by its histologic polymorphism which, on the whole, is that of an inflammation and not that of a tumor. Xanthogranuloma forms the anatomic substratum of Hand-Rowland (Schüller-Christian) disease, but it may also be observed other than in this condition, in various regions of the body. A characteristic localization appears to be that in the retroperitoneal space, where the xanthogranuloma may extend widely and simulate a tumor of considerable size. Three such cases are described together with the cases previously published in the literature.

FROM THE AUTHOR'S SUMMARY.

CONDITIONS INDUCED BY OESTROGENIC COMPOUNDS IN THE COAGULATING GLAND AND PROSTATE OF THE MOUSE. H. BURROWS, Am. J. Cancer **23**:490, 1935.

The prolonged administration of estrin to mice causes hyperplasia and metaplasia in the prostate. The prostate undergoes similar changes in children before birth, presumably under the influence of estrin derived from the placenta. Both in mice and in new-born children the prostatic changes thus induced are completely reversible, restitution to the normal state following a cessation of the supply of estrin. The changes found in benign enlargement of the human prostate in advanced life resemble in character and situation those observed in mice under the influence of estrin and in new-born babies. The question is discussed whether the benign enlargement of the prostate in elderly men may be due to the action of estrogenic hormones and may be a reversible condition.

FROM THE AUTHOR'S CONCLUSIONS.

EXTRAMEDULLARY PLASMA-CELL TUMORS OF THE UPPER AIR PASSAGES. W. L. MATTICK and A. A. THIBAUDEAU, Am. J. Cancer **23**:513,–1935.

A case of plasma cell tumors apparently neoplastic occurring simultaneously in the nasopharynx and hypopharynx, is described. In the nineteen instances previously reported by other observers the plasma-cell tumor has been variously interpreted as granulomatous, inflammatory, benign or malignant. The details of these cases are presented in tabular form. The occurrence of polypoid growth of single or multiple nature in the upper air passages with a history of long duration should arouse suspicion of a plasma cell tumor. The use of the x-rays aids in diagnosis. It is believed that the tumors reported are unusual and dissimilar from most of the tumors previously reported in that they are definitely neoplastic.

FROM THE AUTHORS' SUMMARY.

GRANULOSA-CELL TUMORS OF THE OVARY. H. C. THORNTON, Am. J. Cancer **23**:522,–1935.

A case of granulosa cell tumors in a 63 year old woman six years past the menopause is described. There was a history of vaginal bleeding beginning about one year after the cessation of menstrual bleeding and continuing intermittently for four years, then becoming almost continuous for about a year. Examination revealed a large uterus and a movable pelvic mass. At operation a right ovarian tumor 6 cm. in diameter, the right tube and the body of the uterus were removed. The ovarian tumor proved to be a typical granulosa cell tumor showing folliculoid, cylindromatous and diffuse areas. The histologic structure was predominantly cylindromatous. Grossly, the tumor was practically solid, showing only a few small cysts. The uterus was greatly hypertrophied, and the endometrium showed marked glandular-cystic hyperplasia. There was also an adenomyoma of the uterus. The urine collected over a period of thirty-one hours, beginning twenty-four hours after the operation, was shown to contain folliculin. The diagnosis of granulosa cell tumor in this case rests on the morphologic characteristics of the tumor, the evidence of follicular hormone activity in a woman six years past the menopause presented by the large uterus, hyperplastic endometrium and history of uterine bleeding, and the demonstration of folliculin in the urine.

FROM THE AUTHOR'S SUMMARY.

EFFECT OF GOITER-PRODUCING DIETS ON THE GROWTH OF CARCINOMA, SARCOMA AND MELANOMA IN ANIMALS. K. SUGIURA and S. R. BENEDICT, Am. J. Cancer **23**:541, 1935.

In all groups of animals fed on a goitrogenous diet or the same diet containing added iodine (80, 8,000 or 800,000 γ per hundred grams of food) the rate of tumor growth was slow. This was probably due to the impairment in the health of the animals produced by the faulty diet irrespective of the iodine content. The per-

centage of tumor takes and tumor regressions was found to vary significantly with variation of the iodine content of the diets. The lowest number of takes and the greatest number of tumor regressions occurred in those animals receiving a normal amount of iodine, while animals on either high iodine or low iodine diets showed a high percentage of takes and a low percentage of regressions. Prolonged feeding of the high iodine diets (the animals were fed a normal, well balanced diet containing excessive amounts of potassium iodide) had no therapeutic effect on the growth of Flexner-Jobling rat carcinoma, mouse sarcoma 180 and Pasey mouse melanoma.

FROM THE AUTHORS' SUMMARY.

THYROID ADENOMA IN EXPERIMENTAL ANIMALS. C. A. HELLWIG, Am. J. Cancer **23**:550, 1935.

For the first time in North America thyroid adenomas have been observed in white rats receiving a calcium-rich goitrogenous diet. Thyroid nodules originate not from fetal rests, but from differentiated thyroid epithelium. They are due to the same stimulus which causes diffuse hyperplasia. Thyroid nodules, after reaching a certain size, show all the characteristics of true adenomas. They represent an intermediate stage between hyperplasia and malignant tumor.

FROM THE AUTHOR'S SUMMARY.

ADAMANTINOMAS OF THE HYPOPHYSEAL STALK AND SPHENOID BONE. H. ZEITLIN, Am. J. Cancer **23**:729, 1935.

Tumors of the hypophyseal stalk arise from a definite location but may show histologic differences. They may present a typical arrangement of the epithelial elements and then are usually classified as adamantinoma; some may present atypical enamel formation; others display evidence of malignancy. Cystic degeneration is usually a predominant histologic feature. Clinically the foregoing types cannot be differentiated, but a general diagnosis of an extrahypophyseal tumor can be made.

FROM THE AUTHOR'S CONCLUSION.

ENTDIFFERENTIATION IN BRONCHOGENIC CARCINOMA. P. C. SAMSON, Am. J. Cancer **23**:741, 1935.

In a review of microscopic entdifferentiation in thirty-four cases of primary bronchogenic carcinoma it has been shown that it is possible to arrange these cases in a series with progressive gradations from the most highly differentiated types to those showing extreme entdifferentiation. In the arrangement of the series three fundamental neoplastic cell types have been used: the columnar cell (adenocarcinoma), the squamous cell and the undifferentiated cell carcinoma. When the columnar cell and squamous cell carcinomas are arranged in separate series as to progressive entdifferentiation they approach a common type in which it is no longer possible to distinguish the parent cell. Below this level of differentiation the histologic picture closely resembles that of sarcoma. Cell type in bronchogenic carcinoma depends on the kind and degree of differentiation attained, and not on the level of origin in the respiratory tract. For each of the twenty cases not previously reported a brief description of cell type and extent of metastasis has been given.

FROM THE AUTHOR'S SUMMARY.

THE RELATION OF CELL TYPE TO METASTASIS IN BRONCHOGENIC CARCINOMA. P. C. SAMSON, Am. J. Cancer **23**:754, 1935.

A survey was made of 100 cases of bronchogenic carcinoma in which there were complete autopsies with adequate microscopic control. These were classified as to cell type and 51 per cent were found to exemplify columnar cell (adenocarcinoma), 30 per cent squamous cell and 19 per cent undifferentiated cell carcinoma. A comparison of the reported metastases in the three groups was made by the

method of coefficients of association, and it was found that each group presented certain general characteristics. Adenocarcinoma showed a strong tendency to involve the central nervous system, adrenals, kidneys, both lungs and to some extent the liver. This is best explained on the basis of predominant hematogenous metastasis, with involvement also of the thoracic and abdominal lymph nodes. Squamous cell carcinoma showed a marked tendency to local extension rather than to widespread metastasis, involving the pericardium and bronchial lymph nodes to some extent. In 24 per cent of the cases of squamous cell carcinoma no pulmonary metastases were found. Because of the tendency to local extension this group would appear to offer the best prognosis for radical removal. Judged from the type of organ involved, the small cell carcinoma showed little tendency to hematogenous metastasis. The neoplasms in this group showed extensive lymphogenous metastases, however, associated with involvement of the pancreas, liver and spleen. Because of the differences in the type and extent of growth and of metastases, knowledge of the cell type and of the degree of differentiation can be of aid to the clinician in determining the most advisable course of treatment. Such knowledge should obviously be used in conjunction with the physical examination, history and roentgenographic study. FROM THE AUTHOR'S SUMMARY.

A GLIOMA IN A DOG AND A PINEALOMA IN A SILVER FOX (VULPES FULVUS). C. F. SCHLOTTHAUER and J. W. KERNOHAN, Am. J. Cancer **24**:350, 1935.

GROWTH-PROMOTING AND GROWTH-INHIBITING SUBSTANCES FROM NORMAL ORGANS. J. MAISIN and Y. POURBAIX, Am. J. Cancer **24**:357, 1935.

The tissues of the liver, pancreas and intestinal mucosa promote growth of cancer in tarred mice. The brains, thymus, bone marrow, dried gastric mucosa and dried lymph nodes exert an inhibitive action on the development of tar cancer. The same organ—brain, for example—may contain both growth-inhibiting and growth-promoting factors. The growth-promoting substances are for the most part soluble in water at p_H 7 and p_H 8.4 and are relatively insoluble in ether, being extracted by the latter solvent in only small quantities, with the exception of cholesterol. The growth-inhibiting substances are soluble in ether or are removed by it. They are relatively insoluble in acetone, the soluble portion being precipitated by calcium. The antianemic factor added to the diet in pure form has no influence on growth of tar cancer. FROM THE AUTHORS' CONCLUSIONS.

THE HORMONAL ORIGIN OF UTERINE FIBROIDS: AN HYPOTHESIS. J. T. WITHERSPOON, Am. J. Cancer **24**:402, 1935.

Pathologic and clinical evidence is offered to support a hypothesis that there exists a cause and effect relationship between the unopposed and persistent action of the estrogenic principle produced by multiple follicular cysts of the ovaries on the uterine endometrium and myometrium and the production of immediate endometrial hyperplasia and (provided the stimulation is sufficiently prolonged) more latent uterine fibroids. Since this estrogenic principle affects the genital tract as a whole and also controls the development of the mammary glands it appears that this same hormonal stimulation is the factor initiating endometrioma and fibro-adenoma of the breast. FROM THE AUTHOR'S CONCLUSIONS.

HYPERPROTEINEMIA IN MULTIPLE MYELOMA. ALVIN G. FOORD, Ann. Int. Med. **8**:1071, 1935.

In four cases of multiple myeloma, profound autohemagglutination of the red cells occurred in dry and wet films, and difficulty was encountered in counting erythrocytes in two cases because of granule formation in the pipet. Hyperproteinemia was proved to be present in three cases and was apparently present in the fourth, and seemed to be the cause of these abnormal phenomena. Renal

insufficiency apparently resulted from plugging of the glomerular capillaries by inspissated protein and possibly by the clumping of erythrocytes or changes in osmotic pressure due to the increased protein. Intravascular clumping was demonstrated during life by ophthalmoscopic examination of the retinal veins in one case when pressure sufficient to slow down the circulation was applied externally on the eyeball. Prolonged uncontrollable bleeding and clotting time and increased calcium content of the serum with little change in the platelet count occurred in two cases. The findings of marked rouleaux formation in the smears in two of the cases led to procedures finally indicating the diagnosis of multiple myeloma. Multiple myeloma with resultant renal abnormalities should be suspected in cases of atypical nephritis. FROM AUTHOR'S SUMMARY (FRANK R. MENNE).

LIPOMA OF INTESTINE. J. D. KIRSCHBAUM, Ann. Surg. **101**:726, 1935.

In 5,754 autopsies lipoma of the intestine was found 9 times. In 7 of these cases the lipoma measured from 1 to 3 cm. in diameter; in 1 case it became detached and caused obstruction of the ileum; in the remaining case the lipoma caused intussusception of the lower part of the ileum into the cecum.

ORIGIN AND NATURE OF PIGMENTED NEVI (SCHWANNOMAS). S. W. BECKER, Arch. Dermat. & Syph. **30**:779, 1934.

Examination of several hundred pigmented nevi by modern histologic methods showed that they consisted of one or two types or a combination of both types. The first type is strictly cellular and results from the multiplication of the clear cells in the epidermis with or without penetration into the dermis; the second type is of nerve origin and is deeper, with structures which often simulate those of tactile corpuscles. The use of the term "schwannoma," as suggested by Masson, is not illogical, although more work must be done before the origin of clear cells and of nevi from the sheath of Schwann can be proved. The term "nevus" and "nevoid" are ambiguous and could be replaced by the term "prenatal" without losing any of their significance. FROM THE AUTHOR'S SUMMARY.

LEUKEMIC SINUS RETICULOSIS (MONOCYTIC LEUKEMIA). R. B. HAINING, S. KIMBALL and O. W. JANES, Arch. Int. Med. **55**:574, 1935.

The venous sinuses of the spleen and of the bone marrow and the lymph sinuses of the spleen and of the lymph glands probably are lined by differentiated reticular cells. These cells are similar to the Kupffer cells of the liver. Like the Kupffer cells, they are entirely different from the endothelial cells lining the ordinary blood and lymph channels. The term "reticulo-endotheliosis" applied to monocytic leukemia does not elucidate the fact that the endothelial cells lining the ordinary blood and lymph vessels have nothing to do with the process. Neither does it attempt to distinguish between true reticulum and sinus reticulum (reticulo-endothelium). Monocytic leukemia is probably a sinus reticulosis, whereas myeloid and lymphoid leukemia are probably true reticuloses. There are good grounds for the conception that leukemia is a malignant neoplastic process. Malignant processes and neoplasia are closely associated in our minds with infiltration and with tumor formation. Specific localization with tumor formation is apparently infrequent in leukemic sinus reticulosis (monocytic leukemia). A case is recorded of acute monocytic leukemia in a young woman with localized mucosal and submucosal reticulosis in the rectal wall which assumed the proportions of a tumor. The tumor produced complete intestinal obstruction; clinically, the case exactly simulated carcinoma of the rectum with intestinal obstruction.

FROM THE AUTHORS' SUMMARY.

Society Transactions

LOS ANGELES PATHOLOGICAL SOCIETY

Regular Meeting, March 12, 1935

A. G. Foord, *President, in the Chair*

J. W. Budd, *Secretary*

Pathology of Vaginitis Due to Trichomonas. John F. Kessel and James A. Gafford Jr.

Seventy cases of vaginitis in which the classic clinical symptoms of vaginitis due to Trichomonas were exhibited and the flagellate Trichomonas vaginalis was recovered were observed in this study. Clinically, the walls of the vagina were usually found to be injected and tender, presenting in some instances hyperemia and often minute points of hemorrhage. In the more advanced cases granular areas were prominent. Sections of biopsy material taken from these hemorrhagic and granular areas in forty cases were studied with special reference to the tissue changes and the presence or absence of the trichomonads in the lesions.

The surface in some areas was covered with coagulated material in which trichomonads, white cells and red cells were commonly found. The surface epithelium was usually intact but in certain areas showed erosion, with flagellates between the cells. Areas of hemorrhage were also occasionally observed to break through the surface epithelium.

In the mucosa were areas of infiltration containing collections of lymphocytes, a few polymorphonuclears and an occasional plasma cell. These areas showed increased vascularity and hemorrhage and extended in some instances through the surface epithelium. At times definite necrosis occurred within these areas. Usually it was not possible to find trichomonads in the areas of early infiltration, while in the definitely necrotic regions flagellates were present, and in one case in which the epithelium was entirely eroded they were found in the deeper non-necrotic tissues.

These observations indicate that the pathologic changes are not brought about by simple invasion of the flagellates from the mucosal surface, but that some other mechanism, either toxic or bacterial, is responsible for the primary change of tissue, or that the flagellate is conveyed by the blood stream to the areas of infiltration and ultimate necrosis.

Bacteriologic studies of the vaginal exudate from thirty of the patients with vaginitis and of the secretion from twelve normal persons showed streptococci of the alpha type and also diphtheroids to be present in the secretions of the majority of the normal persons, as well as in the exudates from patients with trichomonad vaginitis. Aciduric bacteria, presumably of the Döderlein type, were found less frequently in the patients with vaginitis than in the normal persons. Gram-negative rods of the colon bacillus type were found in 25 per cent of the cases.

Transplanting exudate containing both T. vaginalis and bacteria from patients with vaginitis to three normal volunteers has resulted in the occurrence of typical symptoms and in recovering Trichomonas from all of the volunteers. Implanting cultures of T. vaginalis and the bacteria with which they grew also produced typical symptoms in two of the three volunteers. In one, the bacteria alone produced mild symptoms of vaginitis.

Attempts to establish Trichomonas of the human intestine in the human vagina have met with negative results. Attempts to establish T. vaginalis in the intestinal tracts of kittens have been negative, although Trichomonas intestinalis of man may be transmitted to kittens. These observations support the theory that the trichomonads of the vagina and the trichomonads of the intestine are distinct species.

TETANY IN A SIX WEEK OLD INFANT. C. M. HYLAND.

A 6 week old boy with a history of convulsions that started when he was approximately 5 weeks of age was admitted Jan. 21, and died Jan. 25, 1935. Birth had been normal with a gestation period of eight months. The weight at birth was 8 pounds and 2 ounces (3,685.4 Gm.). The infant was breast fed for the first month and progressed normally for about five weeks, until the convulsions started. The convulsions were described by the parents as follows: The child would shake violently and draw up all extremities, and in the intervals would sleep deeply. The convulsions occurred only in the evening hours. The family history was not relative. Four other children were alive and well.

The patient appeared physically normal except that the head had a peculiar feel interpreted as that of craniotabes. The tuberculin test was negative. The blood showed: hemoglobin, 66 per cent; red blood cells, 3,010,000; white blood cells, 10,600; polymorphonuclears, 27 per cent; lymphocytes, 55 per cent; monocytes, 14 per cent; eosinophils, 2 per cent; promyelocytes, 2 per cent. The spinal fluid had a trace of globulin but was normal otherwise. The blood calcium was 6.8 mg. per hundred cubic centimeters of serum and the blood phosphorus 7.6 mg. per hundred cubic centimeters of whole blood. X-ray pictures of the head and wrists revealed nothing of importance.

While the boy was in the hospital, many convulsions were noted and he was given 10 Gm. of calcium chloride daily, with considerable symptomatic relief. The convulsions became much less severe but did not entirely cease.

The convulsions were not typical of tetany, as carpopedal spasm was not observed. However, the condition was regarded as tetany associated with rickets regardless of the negative roentgen report. While there was improvement following calcium therapy the course continued to be downhill, and the child died four days after admission.

The only gross pathologic observations at autopsy were acute follicular colitis of a minor degree, hyperplasia of the mesenteric lymph glands and acute hyperplasia of the spleen. The brain was normal. The craniotabes thought to be present was not verified by autopsy or by x-ray picture.

Microscopic examination showed no irregularity of the zone of ossification in the costochondral and costospinal regions. The primary and secondary zones of ossification were normal. The organs of the neck were removed *en masse*, and multiple serial sections were made of the thyroid and of the thyroid portion of the trachea. In all, 1,500 sections were examined for the presence of parathyroid bodies, and two such bodies were recognized, a larger one embedded in the thyroid gland, measuring 250 microns in greatest diameter, and a smaller one embedded in the tissue surrounding the trachea, measuring 50 microns in greatest diameter. The former appeared normal, but the smaller one showed marked vacuolation of the cells.

The features supporting the view that the spasmodic attacks and death were of the nature of tetany due to parathyroid aplasia are: (1) the extremely small amount of parathyroid tissue compared with the normal; (2) the absence of any other recognized causes of tetany, including rickets, which was ruled out by microscopic examination of the bones; (3) the abnormally low blood calcium and high blood phosphorus, and (4) the symptomatic relief following the administration of calcium.

Tetany due to aplasia or absence of parathyroid tissue is unusual, and it is for this reason that the case is presented.

PATHOGENESIS AND PATHOLOGIC ASPECTS OF OTOGENOUS INTRACRANIAL LESIONS. CYRIL B. COURVILLE and J. M. NIELSEN.

Many problems concerned with the intracranial extension of infection in the middle ear and mastoid are as yet unsolved. With some of these problems in mind, we reviewed the records of 10,000 consecutive autopsies. There were 51 instances of otogenous dural infection (2 of chronically thickened dura, 19 of

extradural abscess, 6 of pachymeningitis, 17 of subdural abscess and 7 of dural fistula), 69 instances of thrombosis of venous channels (35 of the lateral sinus, 9 of the cavernous sinus, 8 of the superior longitudinal sinus, 4 of the superior petrosal sinus, 3 of the inferior petrosal sinus and 10 of cerebral veins), 128 instances of septic meningitis (89 primary and 39 secondary), and 35 instances of encephalic abscess (17 of the temporal lobe, 12 of the cerebellum, 3 of the parietal lobe and 3 of the frontal lobe). The 283 lesions were found in 167 cases. The incidence and description of the various lesions we have reported in other contributions (Courville, C. B., and Nielsen, J. M.: *Arch. Otolaryng.* **19**:451, 1934; *Acta oto-laryng.* **21**:19, 1934; *Arch. Surg.* **30**:930, 1935).

One interesting aspect of the complications of otitis media is the seasonal variation in their incidence. For example, in the fiscal year 1929-1930, in 859 autopsies, complications of otitis were found in 63 (7.3 per cent), 32 (51 per cent) being extracranial and 31 (49 per cent) intracranial. Reports of only 4 cases of thrombosis of venous channels were found. In 1932-1933, in 1,414 autopsies, complications of otitis media were found in 109 (7.8 per cent), 67 (61 per cent) being extracranial and 42 (39 per cent) intracranial. There were reports of 15 cases of thrombosis of venous channels in this year, almost four times as many instances in less than twice the number of autopsies.

One indication of an extension of infection to the cerebrum is jacksonian seizures usually of the opposite arm and side of the face, at times followed by weakness or actual paralysis of the affected members. This syndrome is particularly frequent in children (Courville, C. B., and Nielsen, J. M.: *Am. J. Dis. Children* **49**:1, 1935). In older persons these symptoms frequently follow thrombosis of the lateral sinus. The cerebral lesion is located in the region of the central sulcus and may be a temporary local ischemia and edema, actual softening or an abscess. When these symptoms precede those indicative of meningitis, it is likely that the meningeal infection began in this region. Since in a number of cases these symptoms follow thrombosis of the lateral sinus, it is likely that they are due to retrograde extension along the inferior communicating vein (anastomotic vein of Labbé) to the central region. It is furthermore likely that retrograde extension along the communicating system of venous channels accounts for the location of abscesses in the frontal, parietal and occipital lobes, rather than metastasis via the general circulation, even though these channels are not grossly occluded.

The possibility of the development of a subdural abscess secondary to otitis media is coming to be more widely recognized. In this series of autopsies 17 cases of otogenous subdural abscess were found. These may be due (1) to direct spread of infection by contiguity through bone and dura into either the middle or the posterior fossa, (2) to retrograde extension along venous channels or (3) to spontaneous or traumatic rupture of an encephalic abscess in the subdural space. Only when subdural collections of pus become large and when they are uncomplicated with other lesions do they constitute a diagnostic and therapeutic problem.

More study needs to be given to the pathogenesis of abscess of the brain. Three anatomic types have been described: (1) the small, heavily encapsulated abscess, (2) the larger circumscribed abscess with thin capsule and (3) the diffuse abscess (suppurative encephalitis). Any of these three types may occur in the cerebellar white substance as well, and, in addition, small or large interfoliar abscesses may occur. One type of abscess is largely preventable—the postoperative or so-called traumatic abscess. In this case the exploring needle has made its approach through an infected field and carried the infection into the brain. Such a lesion is to be thought of when symptoms of an abscess arise shortly after an exploration.

MIXED TUMOR OF FUNDUS UTERI. ALVIN G. FOORD.

Twenty-three cases of mixed tumors of the body of the uterus, including instances of the tumor diagnosed as rhabdomyosarcoma, have been reported in the literature. Most of these have shown embryonic striated muscle, and about a third

have shown glands, cartilage or rarely other structures such as bone, fat or nerve tissue. The following case was clinically and pathologically similar to most of the cases reported in that the tumor occurred in a woman past the menopause, was a polypoid growth, recurred soon after removal, did not respond to radiation, and was formed in the greater part of embryonic striated muscle.

A woman, aged 59, the mother of four children, four years past the menopause, consulted her physician for uterine bleeding of about three weeks' duration. Just before admission to the hospital she suffered labor-like pains in the pelvis. The uterus was moderately diffusely enlarged. From a markedly dilated external os a large soft polypoid growth with a necrotic tip protruded. The uterus above the portio vaginalis cervicis was removed the following day. The pelvic lymph nodes and the tubes and ovaries were free from change. The uterus was symmetrical and measured 11 by 9 by 6 cm. The endometrial cavity was dilated and filled by a tumor mass 10 by 9 by 7 cm., which arose, by a narrow pedicle about 1.5 cm. across, from the midportion of the posterior wall of the fundus. Cut surfaces showed no gross extension into the thinned musculature of the fundus. The surfaces were soft, glistening white and homogeneous except for a few areas of hemorrhage or necrosis, chiefly in the distal end.

Microscopically, large areas of the tumor were composed of edematous myxomatous tissue and others of interlacing spindle cells with little or no intercellular matrix. Most of these cells contained hyperchromatic nuclei, and mitoses were frequent. In sections stained with hematoxylin and eosin, and especially in those prepared with iron-hematoxylin stains, cross-striations of some of the cells could be seen. In addition, many huge cells were found with single or multiple nuclei; in many of these, interlacing small fibers showing cross-striations were prominent; in some, only a highly eosinophilic granular cytoplasm was found. Strewn throughout part of the tumor were small nests of hyaline cartilage and gland groups or single bizarre glands composed of cells differing moderately in size and shape and showing hyperchromatic nuclei. These had no connection with the endometrium. Invasion of the uterine muscle was found in the base of the tumor.

A recurrence of the tumor occurred within three months, and when the patient was seen five months after operation, a large mass was palpable above the pubic brim. Treatment with x-rays of high voltage in large doses was given for six weeks with no response. The patient died seven months after first being seen.

At autopsy a huge tumor, 21 by 17 by 16 cm., filled the entire pelvis, and a continuation extended nearly to the umbilicus. There were metastases in the iliac and periaortic and peripancreatic lymph nodes and a few implants on the visceral peritoneum, but there was no involvement of the lungs or liver. Four small nodules were found in the thyroid. Microscopically, the metastases were entirely rhabdomyosarcomatous. No cartilage or glands were seen. Spindle cells with and without striations, similar to those in the original growth, were abundant. They apparently represented embryonic striped muscle cells too immature to show striations.

PHILADELPHIA PATHOLOGICAL SOCIETY

HERBERT L. RATCLIFFE, *Secretary*

May 9, 1935

MORTON MCCUTCHEON, *President, in the Chair*

AYERZA'S DISEASE. D. R. COMAN.

A white woman, aged 35 years, entered the Hospital of the University of Pennsylvania on April 20, 1935. In 1927, eight days after appendectomy and right oophorectomy, she contracted pneumonia, and never thereafter entirely regained health. She complained of pain in the back, which had persisted for some time, and

of a sore throat. In December 1934 she had had a cold, and since that illness she had noted progressive somnolence, dyspnea and headaches. The blood pressure was 130 systolic and 90 diastolic; the erythrocyte count was 8,120,000 with hemoglobin 124 per cent, and the leukocyte count was 7,500. The heart was enlarged, and a rough systolic murmur was heard over the pulmonary area.

The patient rapidly became worse, dyspnea increasing and the blood pressure falling. On May 3 paralysis of both legs with loss of pain and touch sensation developed, and death occurred within a short time.

At autopsy the body was that of an obese white woman of plethoric habitus, weighing 65 Kg. and measuring 160 cm. in length.

The heart weighed 390 Gm. The right auricle was greatly dilated and engorged with blood. The walls of the right and left ventricles were of equal thickness, 1.3 cm., and the apex was formed by the right ventricle. The aortic valve was of the bicuspid type, and the cusps contained calcific plaques.

The aorta was apparently smaller than normal, as were its main branches. It presented yellow intimal thickenings, but no definite gross signs of syphilis. Just distal to the origin of the left subclavian artery, the aorta presented a constriction which barely permitted the little finger to enter its lumen. The pulmonary artery presented several calcareous plaques just above the valvular cusps.

The lungs were partially collapsed. They had emphysematous borders and a subcrepitant doughy consistency. Cut surfaces exposed very prominent vascular structures. The smaller and medium-sized ramifications of the pulmonary arteries stood elevated above the rest of the lung surface as gaping tubes. Their walls were somewhat thickened. The larger vessels were dilated.

At the site of the right ovary there was a small cyst attached by a twisted pedicle. The right ovarian vein was thrombosed near its lower extremity.

The spinal cord showed a thrombosis of the posterior spinal artery.

The gross anatomic diagnosis was Ayerza's disease.

Microscopic examination of the lungs revealed striking changes in the blood vessels. Many of the smaller arteries and arterioles showed complete obliteration by fibrosis and hyalinization. Medium-sized branches showed vacuolation of the medial coat, in which muscle fibers and fat were increased. The intima was thickened and in many instances showed infiltration by small round cells. Stains for elastic tissue showed the internal elastic lamina thickened and split, with a general increase in the elastic elements of the vascular wall.

In comparing this case with those that have been described it is found to present the typical features of primary pulmonary sclerosis with hypertrophy of the right ventricle. Clinically, cases of this type are frequently mistaken for polycythæmia vera, as this one was. Interesting here are the additional observations of coarctation of the aorta and thrombosis of the posterior spinal artery.

ENDOMETRIOSIS OF THE APPENDIX. A. R. CAMERO and F. MOGAVERO.

A white woman, aged 23, married, was admitted to the Misericordia Hospital in September 1934 with a chief complaint of pain in the right lower quadrant of the abdomen. She had been well until about a month before admission, when she had her first attack of abdominal pain on the right side. A diagnosis of acute appendicitis was made, and operation was advised, but she refused surgical intervention, and the attack gradually subsided. The pain recurred, however, at irregular intervals. Because of the continuance of the annoying sensation in the appendical area, she finally submitted to operation.

Her menstrual history was normal except that she had missed one period a few weeks before admission to the hospital. Physical examination gave essentially negative results except for slight tenderness in the right lower quadrant of the abdomen. The urine and the blood counts were normal.

At operation (by Dr. George P. Muller) the appendix was found low in the pelvis. Its tip was covered with granulation tissue which bled easily. The uterus was palpated; it was soft and enlarged to the size of a six weeks' pregnancy. The

appendix measured 7 cm. in length and 9 mm. in diameter. The distal fourth was kinked and covered with delicate vascular adhesions. The bulbous distal fourth was firm and on cross-section showed an eccentric thickening of the appendical wall with a markedly contracted lumen, displaced to one side. The serosa covering the rest of the appendix was smooth.

Microscopically, a fairly well circumscribed mass of endometrial tissue was found in the wall of the appendix near its tip, separating the fibers of the muscularis and showing the characteristic decidual reaction of pregnancy.

The convalescence was uneventful. There was no recurrence of abdominal pain; the patient continued normally through the period of gestation and was delivered of a normal full-term child in April 1935.

ABERRANT PANCREATIC AND INSULAR TISSUE IN THE WALL OF THE JEJUNUM. ROBERT W. MATHEWS.

In a colored man, aged 33, who died in the Philadelphia General Hospital of pulmonary tuberculosis with spread by way of the intrapulmonary blood stream, an unidentified lesion was found in the terminal part of the jejunum. It was almond-sized, firm, grayish yellow and covered by intact mucosa and serosa. On microscopic examination this mass was found composed of aberrant pancreatic tissue, the acini being of normal size and appearance, and the ducts numerous and of irregular size and position; several islands of Langerhans were identified. The gland occupied the whole of the submucosa and muscularis; the mucosa and serosa were intact.

The pancreas is derived from the ectoderm of the primitive alimentary tube, beginning about the sixth week, and is formed from two anlagen opposite each other, the dorsal and the ventral pancreas. The dorsal pancreas is the larger and finally forms the body, tail and duct of Santorini. The ventral pancreas forms the head and the duct of Wirsung. The aberrant tissue was probably drawn away from the main mass in the alimentary tube and, with the lengthening of the tube, was carried to the anomalous position. Aberrant pancreatic tissue is said to be a common finding in the stomach and intestines, but in the Philadelphia General Hospital from 1920 to 1934 inclusive (23,543 necropsies) only two other such conditions have been recorded, one occurring in the stomach and the second in the lateral wall of the duodenum.

TUMOR IN THE WALL OF THE JEJUNUM COMPOSED OF PANCREATIC TISSUE. P. R. TROMMER and J. C. SIMPSON.

A white man, aged 32, was admitted to the Montgomery Hospital, Norristown, Pa., on several occasions over a period of fourteen years with severe symptoms of peptic ulcer. On his last admission in April 1934, operation by Dr. Donald M. Headings revealed the healed scar of a duodenal ulcer. A small tumor was found in the antimesenteric wall of the jejunum, 40 cm. from the ligament of Treitz. It was 1.5 by 1 cm. in diameter, light brown and of granular appearance and impinged slightly on the lumen of the bowel.

Posterior gastro-enterostomy and excision of the jejunal tumor were performed. The patient made an uneventful recovery. Since then he has been fairly well with the exception of two mild attacks of abdominal discomfort; these passed off quickly and caused no disability.

Microscopically, the tumor was composed of pancreatic tissue. Islands of Langerhans were not present. A definite duct lined with columnar epithelium was found in that part of the tumor situated beneath the mucous membrane of the jejunum.

INFLAMMATION IN SYPHILITIC AND NONSYPHILITIC RABBITS. JOSEPH D. ARONSON.

Rabbits infected intratesticularly with the Nichols strain of Spirochaeta pallida were given, two months later, intracutaneous injections of tubercle bacilli of the bovine type, staphylococci (Staph. aureus) or india ink. As controls, nonsyphilitic

rabbits were given similar injections. At varying intervals the sites of injection were removed for inspection.

Dr. David Meranze and I noted that in syphilic rabbits the injection of tubercle bacilli induced a perivascular polymorphonuclear infiltration, followed by sharply defined aggregations of mononuclear cells. The lesions resembled those observed in the skin of rabbits infected intracutaneously with S. pallida. Numerous fibroblasts appeared, throughout the experiment, with fewer epithelioid cells. In the nonsyphilitic rabbits the polymorphonuclear infiltration was diffuse, and was followed by the formation of an abscess and later by a sharply defined large tubercle. Numerous epithelioid cells and fewer fibroblasts were observed.

The injection of staphylococci into the skin of a syphilitic rabbit produced an extensive inflammatory reaction with marked edema, followed by an abscess. There was extensive infiltration by polymorphonuclear cells, which were arranged in aggregations in the tissue spaces, followed by a large abscess and slough, with but little granulation tissue. In the nonsyphilitic rabbits the inflammatory reaction was less marked. Sections of skin from these rabbits showed marked infiltration by polymorphonuclear cells and edema, followed by a small abscess and a small amount of granulation tissue seven days after inoculation.

In the syphilitic rabbits given injections of india ink, a well marked inflammatory reaction was observed, and on gross examination the india ink was found distributed irregularly throughout the derma. At first many aggregated polymorphonuclear cells were observed. Later carbon particles were found in mononuclear cells and in fibroblasts, and marked increase of connective tissue followed. On the other hand, in nonsyphilitic rabbits, no gross inflammatory reaction was seen, and on gross examination a sharply defined narrow brown line was noted. Microscopically, a slight cellular infiltration was observed, and the india ink, at first localized, was later found to be somewhat dispersed.

PATHOLOGY OF LYMPHOGRANULOMATOSIS INGUINALIS. FRED W. WEIDMAN.

Anatomically there are two features for the pathologist to follow: 1. There is a rough parallelism with syphilis, i. e., a primary sore (often overlooked), followed by the bubo, with generalization of that disease (eye, spinal fluid) later. 2. The localization of the bubo is contingent on the differing distribution of the lymphatics of the external genitalia of the two sexes. Thus, in females, the extension is generally deep into the pelvis, inducing, among other things, rectal stricture.

As to etiology, the presence of virus appears to be thoroughly established.

Points of immediate practical significance to the pathologist of the general hospital are as follows: 1. Requests for diagnosis are likely to come from the gynecologist and the urologist, as well as from the general surgeon, the internist and the dermatologist. 2. The histologic features are sometimes distinctive, because the architecture of the lymph node is sometimes destroyed; on the other hand, the lesion may consist only of a diffuse round cell infiltration. When abscesses or tubercles are interspersed the picture is at least suggestive and may even be distinctive for lymphogranulomatosis inguinalis. 3. The Frei antigen, which is so specific, is not on the market, and every effort must be made to establish contact with the clinician for the purpose of securing the maximum amount of pus possible with which to make the antigen. Recent reports promise relief from this difficulty through employing brains of experimentally infected monkeys and mice and perhaps also cultures of the virus.

HISTOLOGY OF THE HEMOPOIETIC TISSUES IN HEMOPHILIA. R. P. CUSTER and E. B. KRUMBHAAR.

Three fatal cases of hemophilia in which necropsies were made are reported. One patient died from uncomplicated hemorrhage, one from appendicitis and hemorrhage, and one from fulminating pneumonia. The hematopoietic tissues in all three cases showed normal regenerative ability, in the first two predominantly erythroblastic, in

the third leukoblastic. In all three cases there was a marked increase in megakaryocytes and their progenitors in the bone marrow, indicating a relationship of the blood platelets to the hemophilic process. J. H. Wright's observation of the formation of platelets in the sinusoids of the bone marrow from intruding pseudopods of the cytoplasm of megakaryocytes is supported by our observations.

This work is reported in full in the *American Journal of the Medical Sciences* (**189**:620, 1935).

NEW YORK PATHOLOGICAL SOCIETY

May 23, 1935

WILLIAM C. VON GLAHN, *Presiding*

CARCINOMA OF THE ULTIMOBRANCHIAL BODY. RUBIN POLESHUCK (by invitation).

A 28 year old man, an American, was admitted to the medical service of the Cumberland Hospital on July 31, 1934, with swelling of the neck, anorexia and vague gastro-intestinal disturbances.

The past history of the patient and family history were irrelevant.

Physical examination revealed a blond white man whose face and neck were full but not grossly edematous. The upper part of the chest presented numerous enlarged and tortuous veins. An x-ray film showed a nonpulsating shadow indicative of a tumor in the upper mediastinal area. Under the impression that the condition was Hodgkin's disease, the patient was given roentgen therapy and discharged to the clinic considerably improved, with, however, no decrease in the size of the tumor.

In the clinic he complained of occasional headaches with blurring of vision, stiffness of the neck and dizziness and weakness, which had caused him to fall down on several occasions. Physical examination revealed thrombosis in the external jugular vein on the right side and increased engorgement of all the veins of the chest, neck and arms.

The patient was readmitted to the hospital Jan. 21, 1935, with the added complaint of dyspnea on exertion. Surgical removal of the mass was then attempted, and an inoperable tumor was found. Biopsy resulted in a diagnosis of carcinoma possibly bronchogenic in origin. The patient reacted poorly; pyopneumothorax developed, and death occurred on the tenth day after the operation.

The observations at autopsy were as follows: The anterior and superior mediastinum contained a large encapsulated nodular mass about 15 cm. in diameter. This extended superiorly as far as the thyroid gland, posteriorly almost to the spine and anteriorly to the sternum, to which it was adherent. Inferiorly it extended to the heart, pushing the latter to the left, and laterally it encroached on both pleural spaces (more on the right one), where it was adherent to both lungs.

There was massive thrombosis in both the internal jugular and the subclavian veins, the thrombi extending into the tributaries of both of the arms.

The cut surface of the tumor was variegated, some areas being yellow and others gray or deep red. Some portions were soft; others were firm, and still others almost cartilaginous.

Microscopically, the tumor was made up of two rather definite types of cells. One was an elongated columnar cell, staining dark, which tended in many areas to form acini. The cytoplasm stained deep pink and was smooth. The nucleus varied in shape and size but was usually oval and vesicular. The other type of cell bore a striking resemblance to a plasma cell but was larger. Its cytoplasm was pink and smooth, and its nucleus, eccentric, hyperchromatic and round or oval. Numerous mitotic figures and dividing forms were seen. These cells were arranged in histoid fashion and were separated by a scant fibrovascular stroma.

The tumor as a whole was very vascular, and in some areas it appeared angiomatous, with numerous areas of hemorrhagic extravasation. The walls of the blood vessels were thin. Many vessels contained platelet thrombi, some of which showed hyalinization and calcification. A characteristic feature of the growth was its tendency to invade the lymphatics and blood vessels. In some sections the neoplasm also showed a tendency to grow in strands or groups of deeply staining cells separated by myxomatous and hyaline substance in which were many young fibroblasts. Large portions of the tumor showed degenerative changes and calcium deposition. Other portions showed areas of necrosis with peripheral infiltration by polymorphonuclear cells.

The pericardial sac contained about 1,500 cc. of a cloudy straw-colored fluid. The epicardium was covered by fibrinopurulent exudate. The neoplasm extended into the upper portion of the pericardium.

The right pleural cavity was filled with a large amount of fibrinopurulent exudate compressing the lung.

The posterior mediastinal and supraclavicular lymph nodes were enlarged and on microscopic examination showed metastatic groups and strands of cells similar to those of the main tumor mass.

Although the history of this case as well as the location of the tumor suggests the possibility of a thymic neoplasm, still the histologic structures fail to fulfil the criteria for this type of growth and suggest an origin from an epithelial structure such as a branchial rest. References to this type of neoplasm in the literature are scant. Getzowa, in a study of serial sections of thyroids from idiots and cretins, found many tubular structures and solid groups of cells which histologically belonged neither to the thyroid nor to the parathyroid. These she considered to be rests of the ultimobranchial bodies.

Langhans described five cases of tumor of the ultimobranchial body. In each of these cases the structure of the tumors, he believed, resembled closely the cell groups described by Getzowa.

Ewing also described two cases of a similar tumor which he believed to have originated in the ultimobranchial body, and in our case examination of the gross and microscopic specimens suggested the possibility of a similar origin.

DIFFERENT FORMS OF LEIOMYOSARCOMA UTERI. LOUISE H. MEEKER.

Myoma of the uterus furnishes 50 per cent of all tumors. Less than 2 per cent are malignant. Four specimens differing in gross morphology are presented: (1) a large pedunculated form, (2) a circumscribed lymphangiectatic form, (3) a circumscribed cystic type and (4) a diffuse form. They do not differ in minute histology, and the gross difference seems to depend largely on the situation of the primary focus and its relation to the blood vessels and lymphatics in the associated connective tissue. Types 3 and 4 deserve special mention.

In type 3, the cysts are usually produced by dissolution of connective tissue and accumulation of lymph, which pushes the muscle nodes to the periphery of the tumor. Cavities of the type I am presenting are exceedingly rare. Cullen stated in 1909 that there was only one tumor of this type among 1,674 examples of myoma of the uterus reviewed by him. Hellier in 1914 published a report of such a tumor which he considered remarkable. The inner wall was marked by prominent gyri and was lined by many layers of closely packed smooth muscle cells. Other examples are wanting or are not described in histologic detail. All the cystic forms of this type are described as of the size of a grapefruit.

In type 4, the connective tissue of the myometrium in general shows lymphangiectasis, and the multiple foci of the myoma form ramifying tumor pegs throughout the distended lymphatics (a modification of myoma gyratum?). Few tumors of this type have been reported. There are descriptions of such tumors, but the details are more or less vague. Examples are described in reports of R. Meyer, and several are cited by him. Boyd has said that the type is so rare that it need not be considered. Frank has described similar ramifying growths under the title

"Fibromyomasis—an Unclassified Plexiform Endolymphatic Proliferation of the Uterus." In the one which I show there is no glandular epithelium or mucosal stroma to suggest origin in a previous adenomyoma.

Although these four examples of leiomyosarcoma of the uterus differ in gross structure they are the same in cell type. The neoplastic cell in each instance is a small round or spindle-shaped cell with rounded nucleus and scanty cytoplasm. It does not exhibit polymorphism, and mitotic figures are not abundant. The active cell is a muscle cell of embryonal type, and the connective tissue does not participate in the neoplastic process.

The greatest variation is seen in the degeneration and liquefaction of the connective tissue and the relation of this to the lymph stasis. I find abundant hyaline degeneration and extensive liquefaction in both the tumors and the connective tissue of the general myometrium of the diffuse growths. The myoblasts are most abundant where the lymph is most abundant both in the partly liquefied matrix and in the lymph channels.

One is reminded that the connective tissue of the uterus contains embryonal smooth muscle cells that multiply greatly during pregnancy. That these cell rests may give rise to tumors has been suggested and seems probable. If connective tissue secretes a hormone, as claimed by several investigators, doubtless the extremely labile connective tissue of the uterus has its own type of hormone to balance the hormonal stimulus which promotes activity of uterine muscle, and a change in the drainage and the amount of lymph may upset this balance, allowing one or the other tissue to predominate. Such a condition may be local or under certain circumstances widespread, and multiple tumors arising from the muscle rests may produce the diffuse sarcoma of muscle origin.

DISCUSSION

ALFRED PLAUT: In the last ten years, my associates and I have seen only two examples of leiomyosarcoma of the uterus. I agree with Dr. Meeker that the percentage given in the older literature is entirely too high. One can easily make a test by carefully choosing a high power microscope field of an ordinary cellular myoma uteri and asking a younger pathologist what he calls that. Quite often one will hear the diagnosis sarcoma.

I should like to ask Dr. Meeker whether her last case is supposed to be similar to the case which Dr. Robert T. Frank presented several years ago at the Graduate Fortnight of the New York Academy of Medicine. If I remember correctly, the cells of that tumor, of a kind which I had never seen before, or after, seemed to conform to those of the stroma of the endometrium more than to muscle cells. If I understood Dr. Meeker correctly, I heard her refer to Dr. Frank's case, and I wonder what the relation of these two types of tumor may be. I also should like to ask how far the gross appearance of Dr. Meeker's tumors was suggestive of sarcoma. Did the cut surfaces have the characteristic look of cut crab meat or fish meat?

S. H. POLAYES: Was the endometrium involved in all of these four cases, or just in one?

NATHAN C. FOOT: Can Dr. Meeker give any statistics of the likelihood of metastases? As I understand it, it is extremely rare for sarcoma of this type to metastasize, but one is often confronted by the surgeon who asks about the likelihood of metastases in such cases.

LOUISE H. MEEKER: In reply to Dr. Plaut, I should like to say that I think Dr. Frank intended to convey the idea that the stromal cells of the endometrium were the active cells in his tumor. The cells in such a case are, according to the opinion of Ewing, embryonal muscle cells.

As to the tumors having the characteristic appearance of sarcoma, that is questionable. They looked as though they might be sarcoma, but I do not know that I could say they did positively, except in the case of the diffuse tumor, which certainly suggested sarcoma.

In regard to involvement of the endometrium, there was no involvement of it except from pressure, which produced the polypoid thickenings. The idea that endometrium may have extended into blood vessels, as Sampson thought, to give origin to the tumor of diffuse type and that then the glandular elements were destroyed by pressure does not seem to be borne out here. There was nothing to suggest any relation to the endometrium or to the endometrial stroma. It was all embryonal muscle which produced the active proliferating tumor.

In answer to Dr. Foot, tumors of this type sometimes metastasize, but metastasis is very rare. The surgeons who operated in these cases are questioning what will happen before the end of five years.

LEIOMYOSARCOMA OF THE GALLBLADDER. LOUISE H. MEEKER.

The specimen is presented because of the rarity of muscle sarcoma of the gallbladder. It is from a case included by Dr. John F. Erdmann in his recently published article, "Neoplasms of the Gall Bladder." Few cases of undoubted sarcoma of the gallbladder have been reported. In only a small number of these was the tumor derived from muscle. Gaetani's summary of thirty reputed cases, published in 1932, included only one of leiomyosarcoma. The microscopic picture is that of closely packed large embryonal muscle cells, varying in shape from round to polyhedral, with fairly frequent mitotic figures.

FILTRATION AND SECRETION IN THE HUMAN KIDNEY. HOMER SMITH (by invitation).

It is supposed that the remote ancestor of the vertebrates possessed a tubular kidney draining the body celom, such as is observed in most invertebrates and especially in the annelids. The glomerulus, which is found only in the kidney of the vertebrate, is supposed to have been evolved by some primitive chordate to facilitate the excretion of water from the body. This postulate rests in part on the currently accepted views of renal function and in part on the paleontological evidence that the earliest definitive fishes were inhabitants of fresh water. The first glomerular forms, it should be noted, may well have been in highly organized vertebrates; the postulate does not require, as Chamberlain has suggested, that the first chordates themselves were evolved in fresh water, but only that the special character of the glomerular kidney indicates a fresh water habitat at the time when this character was established.

So long as the organism remained in fresh water (dipnoans, ganoids and teleosts) or in intimate dependence on it (amphibians) this excretory arrangement persisted; but with the secondary assumption of a marine habitat (teleosts) where the osmotic gradient was reversed and the excretion of water reduced, or with the assumption of terrestrial life, in which conservation of water became a necessity (arid-living reptiles and birds), the organism no longer needed and could no longer economically use this primitive water-excreting mechanism. There was thus a need to either (*a*) discard or reduce the glomeruli or (*b*) amend their primitive function by adding distally a more efficient mechanism for the reabsorption of water. The first process appears to be occurring in the marine teleosts and in the reptiles. In the mammals and possibly to some extent in the birds, on the other hand, the addition of the loop of Henle has permitted the reabsorption of water against the osmotic pressure of the metabolites in the urine; consequently in these the glomeruli, although still very active as filters, have become secondarily incorporated into a filtration-reabsorption system which permits the excretion of waste products without the excretion of excessive quantities of water.

In man the quantity of glomerular filtrate (glomerular clearance) is about 100 to 125 cc. per minute. The urea clearance is considerably lower, probably because of reabsorption some place along the tubular system. The creatinine clearance is higher by about 40 per cent, and the phenol red clearance is more than three times as great, in both instances because of tubular excretion from the postglomerular blood. Other substances which are normally absent from the urine (dextrose, creatine, etc.) show an increasing clearance as the level of the plasma is raised.

DISCUSSION

ALFRED PLAUT: Is there a special behavior of the glomerular apparatus of fish which change from sea water to fresh water and vice versa, for instance, the eel, which leaves the depth of the mid-Atlantic and migrates to the estuaries of America and Europe, with the young returning from the rivers to the original place?

HOMER SMITH: Dr. Plaut's question touches subjects which are being investigated. It seems, a priori, that there must be a physiologic mechanism for reducing glomerular activity when fishes go from fresh into salt water. There are observations which indicate that the glomeruli of the eel, in particular, are under physiologic control, but how that control operates, I do not know. It has been suggested for frogs and fish that there are shunts between the afferent and efferent arterioles so that the blood can be sent through without crossing the entire capillary bed. That might be one method. Another method might be that of an ischemia of the kidney. Nothing is known about the details of the mechanism involved, and my associates and I are interested in finding out whether such physiologic mechanisms condition the migration of fish like the eel from fresh water into salt water.

THE THIRD DIMENSION IN PATHOLOGIC INVESTIGATION. JEAN OLIVER (by invitation).

The importance of the third dimension in investigations of morphologic changes in diseased tissues was illustrated by the demonstration of plastic preparations of the abnormal nephrons of the kidney in chronic Bright's disease. These structures were shown in model reconstructions by the Born wax plate method and in microdissections of tissue macerated in strong hydrochloric acid. The various changes that have been observed in the course of the nephron from the glomerulus to the pelvis of the kidney were shown (ARCH. PATH. **15**:755, 1933; **18**:777, 1934; **19**:1, 1935) and attention drawn to the possible use of these methods in the investigation of other morphologic problems.

DISCUSSION

HOMER SMITH: I should like to ask what proportion of glomeruli might still be functioning in the kidney, in a case of extremely severe chronic glomerulonephritis, or what proportion of aglomerular tubules, when the glomeruli are gone: Is it 1 in 100,000, 1 in 1,000 or 1 in 10?

JAMES A. SHANNON: What proportion of the glomeruli in pathologic cases have hypertrophy of Ludwig's vessel? Is it a common thing?

JEAN OLIVER: In regard to the frequency of occurrence of aglomerular tubules I should reply that my associates and I are still working on this problem, and I do not think I am prepared as yet to make a definite statement about it. The answer is complicated by the fact that chronic glomerulonephritis seems to produce two architectural forms of kidney: In one there is a very diffuse change characterized by simple atrophy of the proximal convolutions, and in that form it is only very occasionally that one finds aglomerular tubules. This sort of kidney is usually found when the disease has been fairly rapid in its development, or perhaps it would be better to say, when it shows high intensity throughout its course—when there are no remissions. The other type of kidney is quite different, because the changes are decidedly patchy. There are areas that are similar to what I have described, that is, where atrophy is the outstanding change in the nephrons, but there are other areas in which the nephrons are not only well preserved, but are hypertrophic and hyperplastic. You have all seen these two pictures in sections of kidney showing chronic glomerulonephritis. One is the smooth kidney of Fahr, and the other is the nodular kidney. It is in the latter type, the type in which the disease has gone on for years—the patient has shown remissions, he has been quite ill for long periods of time and then apparently well for weeks or months—

that one finds aglomerular tubules. But I do not think I can give any accurate figure as to what the proportion is, though I can say they are common. One can find them without any difficulty if one looks in one of the better preserved portions of the kidney.

I have the same difficulty in answering the second question as to how frequent the occurrence of Ludwig's vessel is. It is practically impossible to find this vessel in normal kidneys. In fact, in a normal kidney I have never found one that I was certain of. Moreover, there is a practical difficulty in identifying the vessel of Ludwig and this comes from the fact that the afferent vessel may subdivide and go to two or more glomeruli; if one breaks off a branch and does not know one has broken it off, one has something that apparently fulfils the requirements of Ludwig's vessel. The real vessel of Ludwig comes off at almost a right angle from the afferent vessel. If one has been careful, one knows there never was a glomerulus there. If one is fortunate, there are capillaries on the end of the vessel. In that case there is no question but that the finding is Ludwig's vessel. But in the normal kidney it is almost impossible to find an example. In abnormal kidneys it is fairly easy to find examples, but again I hesitate to give a figure. It would mean dissecting several hundred specimens, and one would have to be sure in the several hundred that one had prepared that one had not missed any vessel of Ludwig. Then, of course, if one were sure of one's facts, one could give a statistical figure, but this would be a difficult thing with this technic. I think it is permissible to say that Ludwig's vessel and the aglomerular tubule are found frequently, but I do not think I dare say much more than that.

HOMER SMITH: In the illustration shown do you know whether that instance of Ludwig's vessel goes to the proximal or to the distal tubule?

JEAN OLIVER: It goes to the neighborhood of both. I do not think I can say it goes to one, because the two tubules are so mixed.

Book Reviews

La protidémie et la pression osmotique des protides: Recherches expérimentales et applications cliniques. By Antoine Codounis, Professeur agrégé à la Faculté de Médecine d'Athènes. Preface by Professeur Ch. Achard. Paper. Price, 36 francs. Pp. 212. Paris: Masson & Cie, 1934.

Prior to his appointment at the University of Athens, Codounis was associated with Achard in Paris. He published with Achard and with other collaborators a long series of articles on various aspects of the same subject with which this book deals. This work, which received the prize of the Academy of Medicine in Paris, is a summary of all those publications, with brief references to the work of other authors. Introductions by Achard and Codounis occupy six pages.

The first part, of fifty-five pages, deals with experimental investigations. It begins with a presentation of methods, particularly of the author's own technic of the determination of protein. Then follow discussions: (*a*) of the properties of serum protein and of its fractions; (*b*) of the origin of these fractions and of their relation to the liver, lungs, spleen, kidneys, stomach and thyroid; (*c*) of the influence of cathartics and of thirst on the blood proteins of the dog. Very valuable is the next chapter on the blood proteins in normal animals that are commonly employed for experimental work (the horse, the rabbit, a few species of monkeys, the dog and the guinea-pig). Results of studies dealing with the influence on blood proteins of experimental amyloidosis and experimental intestinal obstruction in the dog, of immunization and of various experimental infections in the horse and of infections in the monkeys are recorded.

The major part of the book, consisting of one hundred and fifteen pages, is devoted to a presentation and analysis of a large mass of data dealing with the variation of blood proteins in various diseases of man. The series includes twenty-two normal healthy persons, twenty pregnant women, ten new-born babies and three hundred and thirty patients afflicted with various diseases. The examinations included an estimation of osmotic pressure, total proteins, albumin, globulin, the albumin-globulin ratio and, in some cases, lipoids and cholesterols. The finding of a reversal of the normal albumin-globulin ratio, owing to a lowering of the total proteins, but particularly of the albumin, in various acute and chronic infectious diseases, confirms a few older reports. In striking contrasts are the normal or slightly elevated values for protein in tuberculous meningitis, while a similar change is present in pulmonary tuberculosis and in other infectious diseases. The prognostic value of the low protein level is illustrated with histories of cases. A study of fifty-one cases of various forms of nephritis and of nephrosis, with the clinical and laboratory data, should prove of value to clinicians and investigators, even if they would not agree with the conclusions of Codounis.

The chapters dealing with the diseases of the heart and blood vessels and of the blood, the liver, the digestive tract, the endocrine glands and the nervous system and with malignant tumors contain valuable observations. Codounis concludes this section with the significant remark that the disturbances of the protein balance are a nonspecific phenomenon similar to the sedimentation reaction of erythrocytes. That impression forces itself all along on the reader. If the different and laborious chemical estimations add little or nothing to the information offered by the simple sedimentation test of erythrocytes, the choice between the two should be easy.

The book closes wih a short chapter on the osmotic pressure of proteins and its significance in pathology. The bibliography lists one hundred and eighty-two titles and is obviously incomplete with regard to German and American publications, among which even fundamental recent articles were omitted. On the other hand, the publications of Achard and of his associates take up about one third of the whole list. The American student of the subject will find the accumulated laboratory data of considerable value, but if he seeks information, according to the

reviewer, he will find more of it, more clearly presented and more easily accessible, in the sixty pages of chapter XIII in the first volume of Peters and Van Slyke's "Quantitative Clinical Chemistry."

The Pathology of Internal Diseases. By William Boyd, M.D., M.R.C.P. (Edin.), F.R.C.P. (Lond.), Dipl. Psych., F.R.S. (Can.); Professor of Pathology in the University of Manitoba; Pathologist to the Winnipeg General Hospital. Second edition, thoroughly revised. Price, $10. Pp. 904, with 335 illustrations. Philadelphia: Lea & Febiger, 1935.

It is a pleasure to welcome the second edition of this book. Major alterations have been made in many sections, and much new material has been added. The references at the end of the chapters are now arranged under subjects in place of alphabetically according to the authors' names, which is of advantage when the titles to articles in periodicals are omitted. "The aim of the present edition has been to develop the subject along clinical and physiological lines even more than to add material which is pathological in the strict sense of morbid anatomy." The scope of the book is best shown by the subjects of its seventeen chapters: diseases of the heart, arteries, respiratory system, stomach and duodenum, intestines, liver and gallbladder, pancreas, kidneys, adrenal glands, thyroid gland, parathyroid glands, pituitary body, blood, bone marrow, spleen, lymph nodes and thymus gland and nervous system. The book consequently covers the field usually included under the term internal medicine, except that acute infectious diseases such as measles, scarlet fever, smallpox, tularemia, undulant fever and whooping cough have not been included. This omission will be a disappointment to many readers. As indicated by the quotation from the preface, the general plan is to discuss the nature, the etiology and the structural changes of internal diseases, with special reference to the relations between the clinical manifestations and the lesions. The illustrations answer their purpose well. The style is clear and fluent. There may be a slight tendency to resort to general phrases to explain obscure phenomena. This is illustrated by the following statement from the section on sudden cardiac death: "Finally there remains a group of cases in which the patient dies of sudden heart failure, but no satisfactory cause can be assigned. Such cases may be put down to shock, status lymphaticus or a visitation from God." And in discussing infectious processes probably too many effects are ascribed offhand to "the action of the toxin." The statement on page 296 that food-handlers constituted the chief danger in the Chicago outbreak of amebic dysentery in 1933 should not be allowed to stand, because the main factor in that outbreak was contamination of the water supply in two hotels. Under heart block (p. 63) it is stated that the course of the conduction system is described at the beginning of the chapter, but it appears that in the revision of the first edition that description has been omitted.

The book is an excellent introduction to the study of clinical medicine and will be of special interest to medical students as they enter clinical work as ward clerks and interns, as well as to physicians who wish to refresh their knowledge of the pathology in the broad sense of internal diseases.

Books Received

A Bibliography of Two Oxford Physiologists: Richard Lower, 1631-1691; John Mayow, 1643-1679. John F. Fulton, M.A. Oxon., Sterling Professor of Physiology in the Yale University School of Medicine. Pp. 62, with 7 figures. London: Oxford University Press, 1935.

The Determination of Iodine in Biological Substances. Medical Research Council, Special Report Series, No. 201. C. O. Harvey. Price, 1 shilling. Pp. 43. London: His Majesty's Stationery Office, 1935.

Forensic Medicine: A Text-Book for Students and a Guide for the Practitioner. Douglas J. A. Kerr, M.D., F.R.C.P.E., D.P.H.; Lecturer on Forensic Medicine in the School of Medicine of the Royal College, Edinburgh; The Police Surgeon and Medical Referee to the City of Edinburgh. Price, $5.50. Pp. 311, with 40 plates, 4 color plates and 30 other figures. London: A. & C. Black, Ltd. (New York: The Macmillan Company), 1935.

A Textbook of Laboratory Diagnosis with Clinical Applications for Practitioners and Students. Edwin E. Osgood, M.A., M.D.; Assistant Professor of Medicine and Biochemistry, Director of Laboratories, University of Oregon Medical School. Second edition. Price, $6. Pp. 585, with 27 text figures and 10 colored plates. Philadelphia: P. Blakiston's Son & Co., 1935.

Agents of Disease and Host Resistance; Including the Principles of Immunology, Bacteriology, Mycology, Protozoology, Parasitology and Virus Diseases. Frederick P. Gay and Associates. Price, $10, Pp. 1581, with 212 figures, 6 color plates and 60 diagrams. Springfield, Ill.: Charles C. Thomas, publisher, 1935.

Human Pathology: A Textbook. Howard T. Karsner, M.D., Professor of Pathology, Western Reserve University. With an introduction by Simon Flexner, M.D. Cloth. Fourth edition, revised. Price, $10. Pp. 1013, with 18 illustrations in color and 433 in black and white. Philadelphia: J. B. Lippincott Company, 1935.

A Textbook of General Bacteriology. Edwin O. Jordan, Ph.D., Professor of Bacteriology in the University of Chicago and in Rush Medical College. Eleventh edition. Cloth. Price, $6. Pp. 825, with 202 illustrations. Philadelphia: W. B. Saunders Company, 1935.

Clinical Parasitology and Tropical Medicine. Damaso de Rivas, B.Sc., Biol., M.S., M.D., Ph.D., Professor of Parasitology in the Graduate School of Medicine and Assistant Professor in the Department of Pathology, University of Pennsylvania. In collaboration with Carlos T. de Rivas, B.A., M.D., Pathologist to the Santo Tomas Hospital, Panama. Price, $5. Pp. 367, with 145 illustrations. Philadelphia: Lea & Febiger, 1935.

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